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(71) Applicant: BASF AKTIENGESELLSCHAFT [DE/DE]; D-67056 Ludwigshafen (DE).

(72) Inventors: POMPEJUS, Markus; Wenjenstrasse 21, D-67251 Freinsheim (DE). KRÖGER, Burkhard; Im Waldhof 1, D-67117 Limburgerhof (DE). SCHRÖDER, Hartwig; Goethestrasse 5, D-69226 Nussloch (DE). ZELDER, Oskar; Rossmarktstrasse 27, D-67346 Speyer (DE). HABERHAUER, Gregor; Moselstrasse 42, D-67117 Limburgerhof (DE). LEE, Heung-Shick; Korea University, Graduate School of Biotechnology, Anam Dong, Sungbook-Gu, Seoul 136-701 (KR). KIM, Hyung-Joon; Korea University, Graduate School of Biotechnology, Anam Dong, Sungbook-Gu, Seoul 136-701 (KR).

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(54) Title: CORYNEBACTERIUM GLUTAMICUM GENES ENCODING STRESS, RESISTANCE AND TOLERANCE PROTEINS

(57) Abstract: Isolated nucleic acid molecules, designated SRT nucleic acid molecules, which encode novel SRT proteins from Corynebacterium glutamicum are described. The invention also provides antisense nucleic acid molecules, recombinant expression vectors containing SRT nucleic acid molecules, and host cells into which the expression vectors have been introduced. The invention still further provides isolated SRT proteins, mutated SRT proteins, fusion proteins, antigenic peptides and methods for the improvement of production of a desired compound from C. glutamicum based on genetic engineering of SRT genes in this organism.

CORYNEBACTERIUM GLUTAMICUM GENES ENCODING STRESS, RESISTANCE AND TOLERANCE PROTEINS

Related Applications

This application claims priority to prior filed U.S. Provisional Patent Application Serial No. 60/141031, filed June 25, 1999, U.S. Provisional Patent Application Serial No. 60/142692, filed July 1, 1999, and also to U.S. Provisional Patent Application Serial No. 60/151214, filed August 27, 1999. This application also claims priority to German Patent Application No. 19930429.7, filed July 1, 1999, German Patent Application No. 19931457.8, filed July 8, 1999, German Patent Application No. 19931457.8, filed July 8, 1999, German Patent Application No. 19931541.8, filed July 8, 1999, German Patent Application No. 19932230.9, filed July 9, 1999, German Patent Application No. 19932230.9, filed July 9, 1999, German Patent Application No. 19932914.1, filed July 14, 1999, German Patent Application No. 19940764.9, filed August 27, 1999, and
German Patent Application No. 19941382.7, filed August 31, 1999. The entire contents of all of the aforementioned applications are hereby expressly incorporated herein in their entirety by this reference.

Background of the Invention

20 Certain products and by-products of naturally-occurring metabolic processes in cells have utility in a wide array of industries, including the food, feed, cosmetics, and pharmaceutical industries. These molecules, collectively termed 'fine chemicals', include organic acids, both proteinogenic and non-proteinogenic amino acids, nucleotides and nucleosides, lipids and fatty acids, diols, carbohydrates, aromatic compounds, vitamins and cofactors, and enzymes. Their production is most 25 conveniently performed through large-scale culture of bacteria developed to produce and secrete large quantities of a particular desired molecule. One particularly useful organism for this purpose is Corynebacterium glutamicum, a gram positive, nonpathogenic bacterium. Through strain selection, a number of mutant strains have been developed which produce an array of desirable compounds. However, selection of 30 strains improved for the production of a particular molecule is a time-consuming and difficult process.

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Summary of the Invention

The invention provides novel bacterial nucleic acid molecules which have a variety of uses. These uses include the identification of microorganisms which can be used to produce fine chemicals, the modulation of fine chemical production in C. glutamicum or related bacteria, the typing or identification of C. glutamicum or related bacteria, as reference points for mapping the C. glutamicum genome, and as markers for transformation. These novel nucleic acid molecules encode proteins, referred to herein as stress, resistance and tolerance (SRT) proteins.

C. glutamicum is a gram positive, aerobic bacterium which is commonly used in industry for the large-scale production of a variety of fine chemicals, and also for the degradation of hydrocarbons (such as in petroleum spills) and for the oxidation of terpenoids. The SRT nucleic acid molecules of the invention, therefore, can be used to identify microorganisms which can be used to produce fine chemicals, e.g., by fermentation processes. Modulation of the expression of the SRT nucleic acids of the invention, or modification of the sequence of the SRT nucleic acid molecules of the invention, can be used to modulate the production of one or more fine chemicals from a microorganism (e.g., to improve the yield or production of one or more fine chemicals from a Corynebacterium or Brevibacterium species).

The SRT nucleic acids of the invention may also be used to identify an organism as being Corynebacterium glutamicum or a close relative thereof, or to identify the presence of C. glutamicum or a relative thereof in a mixed population of microorganisms. The invention provides the nucleic acid sequences of a number of C. glutamicum genes; by probing the extracted genomic DNA of a culture of a unique or mixed population of microorganisms under stringent conditions with a probe spanning a region of a C. glutamicum gene which is unique to this organism, one can ascertain whether this organism is present. Although Corynebacterium glutamicum itself is nonpathogenic, it is related to species pathogenic in humans, such as Corynebacterium diphtheriae (the causative agent of diphtheria); the detection of such organisms is of significant clinical relevance.

The SRT nucleic acid molecules of the invention may also serve as reference points for mapping of the *C. glutamicum* genome, or of genomes of related organisms.

Similarly, these molecules, or variants or portions thereof, may serve as markers for genetically engineered Corynebacterium or Brevibacterium species.

The SRT proteins encoded by the novel nucleic acid molecules of the invention are capable of, for example, permitting C. glutamicum to survive in a setting which is either chemically or environmentally hazardous to this microorganism. Given the availability of cloning vectors for use in Corynebacterium glutamicum, such as those disclosed in Sinskey et al., U.S. Patent No. 4,649,119, and techniques for genetic manipulation of C. glutamicum and the related Brevibacterium species (e.g., lactofermentum) (Yoshihama et al., J. Bacteriol. 162: 591-597 (1985); Katsumata et al., J. Bacteriol. 159: 306-311 (1984); and Santamaria et al., J. Gen. Microbiol. 130: 2237-10 2246 (1984)), the nucleic acid molecules of the invention may be utilized in the genetic engineering of this organism to make it a better or more efficient producer of one or more fine chemicals, through the ability of these proteins to permit growth and multiplication of C. glutamicum (and also continuous production of one or more fine chemicals) under circumstances which would normally impede growth of the organism, 15 such as those conditions frequently encountered during large-scale fermentative growth. For example, by overexpressing or engineering a heat-shock induced protease molecule such that it is optimized in activity, one may increase the ability of the bacterium to degrade incorrectly folded proteins when the bacterium is challenged with high temperatures. By having fewer misfolded (and possibly misregulated or nonfunctional) 20 proteins to interfere with normal reaction mechanisms in the cell, the cell is increased in its ability to function normally in such a culture, which should in turn provide increased viability. This overall increase in number of cells having greater viability and activity in the culture should also result in an increase in yield, production, and/or efficiency of production of one or more desired fine chemicals, due at least to the relatively greater 25 number of cells producing these chemicals in the culture.

This invention provides novel SRT nucleic acid molecules which encode SRT proteins which are capable of, for example, permitting *C. glutamicum* to survive in a setting which is either chemically or environmentally hazardous to this microorganism. Nucleic acid molecules encoding an SRT protein are referred to herein as SRT nucleic acid molecules. In a preferred embodiment, the SRT protein participates in metabolic pathways permitting *C. glutamicum* to survive in a setting which is either chemically or

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environmentally hazardous to this microorganism. Examples of such proteins include those encoded by the genes set forth in Table 1.

Accordingly, one aspect of the invention pertains to isolated nucleic acid molecules (e.g., cDNAs, DNAs, or RNAs) comprising a nucleotide sequence encoding an SRT protein or biologically active portions thereof, as well as nucleic acid fragments suitable as primers or hybridization probes for the detection or amplification of SRTencoding nucleic acid (e.g., DNA or mRNA). In particularly preferred embodiments, the isolated nucleic acid molecule comprises one of the nucleotide sequences set forth as the odd-numbered SEQ ID NOs in the Sequence Listing (e.g., SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7....), or the coding region or a complement thereof of one of these nucleotide sequences. In other particularly preferred embodiments, the isolated nucleic acid molecule of the invention comprises a nucleotide sequence which hybridizes to or is at least about 50%, preferably at least about 60%, more preferably at least about 70%, 80% or 90%, and even more preferably at least about 95%, 96%, 97%, 98%, 99% or more homologous to a nucleotide sequence set forth as an odd-numbered SEQ ID NO in the Sequence Listing (e.g., SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7....), or a portion thereof. In other preferred embodiments, the isolated nucleic acid molecule encodes one of the amino acid sequences set forth as an evennumbered SEQ ID NO in the Sequence Listing (e.g., SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8....).. The preferred SRT proteins of the present invention also preferably possess at least one of the SRT activities described herein.

In another embodiment, the isolated nucleic acid molecule encodes a protein or portion thereof wherein the protein or portion thereof includes an amino acid sequence which is sufficiently homologous to an amino acid sequence of the invention (e.g., a sequence having an even-numbered SEQ ID NO: in the Sequence Listing), e.g., sufficiently homologous to an amino acid sequence of the invention such that the protein or portion thereof maintains an SRT activity. Preferably, the protein or portion thereof encoded by the nucleic acid molecule maintains the ability to increase the survival of C. glutamicum in a setting which is either chemically or environmentally hazardous to this microorganism. In one embodiment, the protein encoded by the nucleic acid molecule is at least about 50%, preferably at least about 60%, and more preferably at least about 70%, 80%, or 90% and most preferably at least about 95%, 96%, 97%, 98%, or 99% or

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more homologous to an amino acid sequence of the invention (e.g., an entire amino acid sequence selected from those having an even-numbered SEQ ID NO in the Sequence Listing). In another preferred embodiment, the protein is a full length *C. glutamicum* protein which is substantially homologous to an entire amino acid sequence of the invention (encoded by an open reading frame shown the corresponding odd-numbered SEQ ID NOs in the Sequence Listing (e.g., SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7....).

In another preferred embodiment, the isolated nucleic acid molecule is derived from C. glutamicum and encodes a protein (e.g., an SRT fusion protein) which includes a biologically active domain which is at least about 50% or more homologous to one of the amino acid sequences of the invention (e.g., a sequence of one of the even-numbered SEQ ID NOs in the Sequence Listing) and has the ability to increase the survival of C. glutamicum in a setting which is either chemically or environmentally hazardous to this microorganism, or possesses one or more of the activities set forth in Table 1, and which also includes heterologous nucleic acid sequences encoding a heterologous polypeptide or regulatory regions.

In another embodiment, the isolated nucleic acid molecule is at least 15 nucleotides in length and hybridizes under stringent conditions to a nucleic acid molecule comprising a nucleotide sequence of the invention (e.g., a sequence of an odd-numbered SEQ ID NO in the Sequence Listing). Preferably, the isolated nucleic acid molecule corresponds to a naturally-occurring nucleic acid molecule. More preferably, the isolated nucleic acid encodes a naturally-occurring C. glutamicum SRT protein, or a biologically active portion thereof.

Another aspect of the invention pertains to vectors, e.g., recombinant expression vectors, containing the nucleic acid molecules of the invention, and host cells into which such vectors have been introduced. In one embodiment, such a host cell is used to produce an SRT protein by culturing the host cell in a suitable medium. The SRT protein can be then isolated from the medium or the host cell.

Yet another aspect of the invention pertains to a genetically altered microorganism in which an SRT gene has been introduced or altered. In one embodiment, the genome of the microorganism has been altered by the introduction of a nucleic acid molecule of the invention encoding wild-type or mutated SRT sequence as

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a transgene. In another embodiment, an endogenous SRT gene within the genome of the microorganism has been altered, e.g., functionally disrupted, by homologous recombination with an altered SRT gene. In another embodiment, an endogenous or introduced SRT gene in a microorganism has been altered by one or more point mutations, deletions, or inversions, but still encodes a functional SRT protein. In still another embodiment, one or more of the regulatory regions (e.g., a promoter, repressor, or inducer) of a SRT gene in a microorganism has been altered (e.g., by deletion, truncation, inversion, or point mutation) such that the expression of the SRT gene is modulated. In a preferred embodiment, the microorganism belongs to the genus Corynebacterium or Brevibacterium, with Corynebacterium glutamicum being particularly preferred. In a preferred embodiment, the microorganism is also utilized for the production of a desired compound, such as an amino acid, with lysine being particularly preferred.

In another aspect, the invention provides a method of identifying the presence or activity of *Cornyebacterium diphtheriae* in a subject. This method includes detection of one or more of the nucleic acid or amino acid sequences of the invention (e.g., the sequences set forth in the Sequence Listing as SEQ ID NOs 1 through 304)) in a subject, thereby detecting the presence or activity of *Corynebacterium diphtheriae* in the subject.

Still another aspect of the invention pertains to an isolated SRT protein or a portion, e.g., a biologically active portion, thereof. In a preferred embodiment, the isolated SRT protein or portion thereof possesses the ability to increase the survival of C. glutamicum in a setting which is either chemically or environmentally hazardous to this microorganism. In another preferred embodiment, the isolated SRT protein or portion thereof is sufficiently homologous to an amino acid sequence of the invention (e.g., a sequence of an even-numbered SEQ ID NO: in the Sequence Listing) such that the protein or portion thereof maintains the ability to increase the survival of C. glutamicum in a setting which is either chemically or environmentally hazardous to this microorganism.

The invention also provides an isolated preparation of an SRT protein. In

preferred embodiments, the SRT protein comprises an amino acid sequence of the invention (e.g., a sequence of an even-numbered SEQ ID NO: of the Sequence Listing).

In another preferred embodiment, the invention pertains to an isolated full length protein

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which is substantially homologous to an entire amino acid sequence of the invention (e.g., a sequence of an even-numbered SEQ ID NO: of the Sequence Listing) (encoded by an open reading frame set forth in a corresponding odd-numbered SEQ ID NO: of the Sequence Listing).). In yet another embodiment, the protein is at least about 50%, preferably at least about 60%, and more preferably at least about 70%, 80%, or 90%, and most preferably at least about 95%, 96%, 97%, 98%, or 99% or more homologous to an entire amino acid sequence of the invention (e.g., a sequence of an even-numbered SEQ ID NO: of the Sequence Listing). In other embodiments, the isolated SRT protein comprises an amino acid sequence which is at least about 50% or more homologous to one of the amino acid sequences of the invention (e.g., a sequence of an even-numbered SEQ ID NO: of the Sequence Listing) and is able to improve the survival rate of C. glutamicum in a setting which is either chemically or environmentally hazardous to this microorganism, or has one or more of the activities set forth in Table 1.

Alternatively, the isolated SRT protein can comprise an amino acid sequence which is encoded by a nucleotide sequence which hybridizes, e.g., hybridizes under stringent conditions, or is at least about 50%, preferably at least about 60%, more preferably at least about 70%, 80%, or 90%, and even more preferably at least about 95%, 96%, 97%, 98,%, or 99% or more homologousto a nucleotide sequence of one of the even-numbered SEQ ID NOs set forth in the Sequence Listing. It is also preferred that the preferred forms of SRT proteins also have one or more of the SRT bioactivities described herein.

The SRT polypeptide, or a biologically active portion thereof, can be operatively linked to a non-SRT polypeptide to form a fusion protein. In preferred embodiments, this fusion protein has an activity which differs from that of the SRT protein alone. In other preferred embodiments, this fusion protein results in increased yields, production, and/or efficiency of production of a desired fine chemical from *C. glutamicum*. In particularly preferred embodiments, integration of this fusion protein into a host cell modulates the production of a desired compound from the cell.

In another aspect, the invention provides methods for screening molecules which modulate the activity of an SRT protein, either by interacting with the protein itself or a substrate or binding partner of the SRT protein, or by modulating the transcription or translation of an SRT nucleic acid molecule of the invention.

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Another aspect of the invention pertains to a method for producing a fine chemical. This method involves the culturing of a cell containing a vector directing the expression of an SRT nucleic acid molecule of the invention, such that a fine chemical is produced. In a preferred embodiment, this method further includes the step of obtaining a cell containing such a vector, in which a cell is transfected with a vector directing the expression of an SRT nucleic acid. In another preferred embodiment, this method further includes the step of recovering the fine chemical from the culture. In a particularly preferred embodiment, the cell is from the genus *Corynebacterium* or *Brevibacterium*, or is selected from those strains set forth in Table 3.

Another aspect of the invention pertains to methods for modulating production of a molecule from a microorganism. Such methods include contacting the cell with an agent which modulates SRT protein activity or SRT nucleic acid expression such that a cell associated activity is altered relative to this same activity in the absence of the agent. In a preferred embodiment, the cell is modulated in resistance to one or more toxic chemicals or in resistance to one or more environmental stresses, such that the yields or rate of production of a desired fine chemical by this microorganism is improved. The agent which modulates SRT protein activity can be an agent which stimulates SRT protein activity or SRT nucleic acid expression. Examples of agents which stimulate SRT protein activity or SRT nucleic acid expression include small molecules, active SRT proteins, and nucleic acids encoding SRT proteins that have been introduced into the cell. Examples of agents which inhibit SRT activity or expression include small molecules, and antisense SRT nucleic acid molecules.

Another aspect of the invention pertains to methods for modulating yields of a desired compound from a cell, involving the introduction of a wild-type or mutant SRT gene into a cell, either maintained on a separate plasmid or integrated into the genome of the host cell. If integrated into the genome, such integration can random, or it can take place by homologous recombination such that the native gene is replaced by the introduced copy, causing the production of the desired compound from the cell to be modulated. In a preferred embodiment, said yields are increased. In another preferred embodiment, said chemical is a fine chemical. In a particularly preferred embodiment, said fine chemical is an amino acid. In especially preferred embodiments, said amino acid is L-lysine.

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Detailed Description of the Invention

The present invention provides SRT nucleic acid and protein molecules which are involved in the survival of *C. glutamicum* upon exposure of this microorganism to chemical or environmental hazards. The molecules of the invention may be utilized in the modulation of production of fine chemicals from microorganisms, since these SRT proteins provide a means for continued growth and multiplication of *C. glutamicum* in the presence of toxic chemicals or hazardous environmental conditions, such as may be encountered during large-scale fermentative growth. By increasing the growth rate or at least maintaining normal growth in the face of poor, if not toxic, conditions, one may increase the yield, production, and/or efficiency of production of one or more fine chemicals from such a culture, at least due to the relatively greater number of cells producing the fine chemical in the culture. Aspects of the invention are further explicated below.

15 I. Fine Chemicals

The term 'fine chemical' is art-recognized and includes molecules produced by an organism which have applications in various industries, such as, but not limited to, the pharmaceutical, agriculture, and cosmetics industries. Such compounds include organic acids, such as tartaric acid, itaconic acid, and diaminopimelic acid, both proteinogenic and non-proteinogenic amino acids, purine and pyrimidine bases, nucleosides, and nucleotides (as described e.g. in Kuninaka, A. (1996) Nucleotides and related compounds, p. 561-612, in Biotechnology vol. 6, Rehm et al., eds. VCH: Weinheim, and references contained therein), lipids, both saturated and unsaturated fatty acids (e.g., arachidonic acid), diols (e.g., propane diol, and butane diol), carbohydrates (e.g., hyaluronic acid and trehalose), aromatic compounds (e.g., aromatic amines, vanillin, and indigo), vitamins and cofactors (as described in Ullmann's Encyclopedia of Industrial Chemistry, vol. A27, "Vitamins", p. 443-613 (1996) VCH: Weinheim and references therein; and Ong, A.S., Niki, E. & Packer, L. (1995) "Nutrition, Lipids, Health, and Disease" Proceedings of the UNESCO/Confederation of Scientific and Technological Associations in Malaysia, and the Society for Free Radical Research -Asia, held Sept. 1-3, 1994 at Penang, Malaysia, AOCS Press, (1995)), enzymes, polyketides (Cane et al. (1998) Science 282: 63-68), and all other chemicals described in

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Gutcho (1983) Chemicals by Fermentation, Noyes Data Corporation, ISBN: 0818805086 and references therein. The metabolism and uses of certain of these fine chemicals are further explicated below.

5 A. Amino Acid Metabolism and Uses

Amino acids comprise the basic structural units of all proteins, and as such are essential for normal cellular functioning in all organisms. The term "amino acid" is artrecognized. The proteinogenic amino acids, of which there are 20 species, serve as structural units for proteins, in which they are linked by peptide bonds, while the nonproteinogenic amino acids (hundreds of which are known) are not normally found in proteins (see Ulmann's Encyclopedia of Industrial Chemistry, vol. A2, p. 57-97 VCH: Weinheim (1985)). Amino acids may be in the D- or L- optical configuration, though Lamino acids are generally the only type found in naturally-occurring proteins. Biosynthetic and degradative pathways of each of the 20 proteinogenic amino acids have been well characterized in both prokaryotic and eukaryotic cells (see, for example, Stryer, L. Biochemistry, 3rd edition, pages 578-590 (1988)). The 'essential' amino acids (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine), so named because they are generally a nutritional requirement due to the complexity of their biosyntheses, are readily converted by simple biosynthetic pathways. to the remaining 11 'nonessential' amino acids (alanine, arginine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, and tyrosine). Higher animals do retain the ability to synthesize some of these amino acids, but the essential amino acids must be supplied from the diet in order for normal protein synthesis to occur.

Aside from their function in protein biosynthesis, these amino acids are
interesting chemicals in their own right, and many have been found to have various applications in the food, feed, chemical, cosmetics, agriculture, and pharmaceutical industries. Lysine is an important amino acid in the nutrition not only of humans, but also of monogastric animals such as poultry and swine. Glutamate is most commonly used as a flavor additive (mono-sodium glutamate, MSG) and is widely used throughout the food industry, as are aspartate, phenylalanine, glycine, and cysteine. Glycine, L-methionine and tryptophan are all utilized in the pharmaceutical industry. Glutamine, valine, leucine, isoleucine, histidine, arginine, proline, serine and alanine are of use in

both the pharmaceutical and cosmetics industries. Threonine, tryptophan, and D/L-methionine are common feed additives. (Leuchtenberger, W. (1996) Amino aids – technical production and use, p. 466-502 in Rehm *et al.* (eds.) Biotechnology vol. 6, chapter 14a, VCH: Weinheim). Additionally, these amino acids have been found to be useful as precursors for the synthesis of synthetic amino acids and proteins, such as N-acetylcysteine, S-carboxymethyl-L-cysteine, (S)-5-hydroxytryptophan, and others described in Ulmann's Encyclopedia of Industrial Chemistry, vol. A2, p. 57-97, VCH: Weinheim, 1985.

The biosynthesis of these natural amino acids in organisms capable of 10 producing them, such as bacteria, has been well characterized (for review of bacterial amino acid biosynthesis and regulation thereof, see Umbarger, H.E.(1978) Ann. Rev. Biochem. 47: 533-606). Glutamate is synthesized by the reductive amination of aketoglutarate, an intermediate in the citric acid cycle. Glutamine, proline, and arginine are each subsequently produced from glutamate. The biosynthesis of serine is a three-15 step process beginning with 3-phosphoglycerate (an intermediate in glycolysis), and resulting in this amino acid after oxidation, transamination, and hydrolysis steps. Both cysteine and glycine are produced from serine; the former by the condensation of homocysteine with serine, and the latter by the transferal of the side-chain \(\beta-carbon atom to tetrahydrofolate, in a reaction catalyzed by serine transhydroxymethylase. Phenylalanine, and tyrosine are synthesized from the glycolytic and pentose phosphate 20 pathway precursors erythrose 4-phosphate and phosphoenolpyruvate in a 9-step biosynthetic pathway that differ only at the final two steps after synthesis of prephenate. Tryptophan is also produced from these two initial molecules, but its synthesis is an 11step pathway. Tyrosine may also be synthesized from phenylalanine, in a reaction catalyzed by phenylalanine hydroxylase. Alanine, valine, and leucine are all 25 biosynthetic products of pyruvate, the final product of glycolysis. Aspartate is formed from oxaloacetate, an intermediate of the citric acid cycle. Asparagine, methionine, threonine, and lysine are each produced by the conversion of aspartate. Isoleucine is formed from threonine. A complex 9-step pathway results in the production of histidine from 5-phosphoribosyl-1-pyrophosphate, an activated sugar. 30

Amino acids in excess of the protein synthesis needs of the cell cannot be stored, and are instead degraded to provide intermediates for the major metabolic pathways of

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the cell (for review see Stryer, L. Biochemistry 3rd ed. Ch. 21 "Amino Acid Degradation and the Urea Cycle" p. 495-516 (1988)). Although the cell is able to convert unwanted amino acids into useful metabolic intermediates, amino acid production is costly in terms of energy, precursor molecules, and the enzymes necessary to synthesize them. Thus it is not surprising that amino acid biosynthesis is regulated by feedback inhibition,

Thus it is not surprising that amino acid biosynthesis is regulated by feedback inhibition, in which the presence of a particular amino acid serves to slow or entirely stop its own production (for overview of feedback mechanisms in amino acid biosynthetic pathways, see Stryer, L. Biochemistry, 3rd ed. Ch. 24: "Biosynthesis of Amino Acids and Heme" p. 575-600 (1988)). Thus, the output of any particular amino acid is limited by the amount of that amino acid present in the cell.

B. Vitamin, Cofactor, and Nutraceutical Metabolism and Uses

Vitamins, cofactors, and nutraceuticals comprise another group of molecules which the higher animals have lost the ability to synthesize and so must ingest, although they are readily synthesized by other organisms, such as bacteria. These molecules are either bioactive substances themselves, or are precursors of biologically active substances which may serve as electron carriers or intermediates in a variety of metabolic pathways. Aside from their nutritive value, these compounds also have significant industrial value as coloring agents, antioxidants, and catalysts or other processing aids. (For an overview of the structure, activity, and industrial applications of these compounds, see, for example, Ullman's Encyclopedia of Industrial Chemistry, "Vitamins" vol. A27, p. 443-613, VCH: Weinheim, 1996.) The term "vitamin" is artrecognized, and includes nutrients which are required by an organism for normal functioning, but which that organism cannot synthesize by itself. The group of vitamins may encompass cofactors and nutraceutical compounds. The language "cofactor" includes nonproteinaceous compounds required for a normal enzymatic activity to occur. Such compounds may be organic or inorganic; the cofactor molecules of the invention are preferably organic. The term "nutraceutical" includes dietary supplements having health benefits in plants and animals, particularly humans. Examples of such molecules are vitamins, antioxidants, and also certain lipids (e.g., polyunsaturated fatty acids).

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The biosynthesis of these molecules in organisms capable of producing them, such as bacteria, has been largely characterized (Ullman's Encyclopedia of Industrial Chemistry, "Vitamins" vol. A27, p. 443-613, VCH: Weinheim, 1996; Michal, G. (1999) Biochemical Pathways: An Atlas of Biochemistry and Molecular Biology, John Wiley & Sons; Ong, A.S., Niki, E. & Packer, L. (1995) "Nutrition, Lipids, Health, and Disease" Proceedings of the UNESCO/Confederation of Scientific and Technological Associations in Malaysia, and the Society for Free Radical Research – Asia, held Sept. 1-3, 1994 at Penang, Malaysia, AOCS Press: Champaign, IL X, 374 S).

Thiamin (vitamin B₁) is produced by the chemical coupling of pyrimidine and thiazole moieties. Riboflavin (vitamin B₂) is synthesized from guanosine-5'-triphosphate (GTP) and ribose-5'-phosphate. Riboflavin, in turn, is utilized for the synthesis of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). The family of compounds collectively termed 'vitamin B₆' (e.g., pyridoxine, pyridoxamine, pyridoxa-5'-phosphate, and the commercially used pyridoxin hydrochloride) are all derivatives of the common structural unit, 5-hydroxy-6-methylpyridine. Pantothenate (pantothenic acid, (R)-(+)-N-(2,4-dihydroxy-3,3-dimethyl-1-oxobutyl)-β-alanine) can be produced either by chemical synthesis or by fermentation. The final steps in pantothenate biosynthesis consist of the ATP-driven condensation of \beta-alanine and pantoic acid. The enzymes responsible for the biosynthesis steps for the conversion to pantoic acid, to βalanine and for the condensation to panthotenic acid are known. The metabolically active form of pantothenate is Coenzyme A, for which the biosynthesis proceeds in 5 enzymatic steps. Pantothenate, pyridoxal-5'-phosphate, cysteine and ATP are the precursors of Coenzyme A. These enzymes not only catalyze the formation of panthothante, but also the production of (R)-pantoic acid, (R)-pantolacton, (R)panthenol (provitamin B_5), pantetheine (and its derivatives) and coenzyme A.

Biotin biosynthesis from the precursor molecule pimeloyl-CoA in microorganisms has been studied in detail and several of the genes involved have been identified. Many of the corresponding proteins have been found to also be involved in Fe-cluster synthesis and are members of the nifS class of proteins. Lipoic acid is derived from octanoic acid, and serves as a coenzyme in energy metabolism, where it becomes part of the pyruvate dehydrogenase complex and the α -ketoglutarate dehydrogenase complex. The folates are a group of substances which are all derivatives

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of folic acid, which is turn is derived from L-glutamic acid, p-amino-benzoic acid and 6-methylpterin. The biosynthesis of folic acid and its derivatives, starting from the metabolism intermediates guanosine-5'-triphosphate (GTP), L-glutamic acid and p-amino-benzoic acid has been studied in detail in certain microorganisms.

Corrinoids (such as the cobalamines and particularly vitamin B₁₂) and porphyrines belong to a group of chemicals characterized by a tetrapyrole ring system. The biosynthesis of vitamin B₁₂ is sufficiently complex that it has not yet been completely characterized, but many of the enzymes and substrates involved are now known. Nicotinic acid (nicotinate), and nicotinamide are pyridine derivatives which are also termed 'niacin'. Niacin is the precursor of the important coenzymes NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate) and their reduced forms.

The large-scale production of these compounds has largely relied on cell-free chemical syntheses, though some of these chemicals have also been produced by large-scale culture of microorganisms, such as riboflavin, Vitamin B₆, pantothenate, and biotin. Only Vitamin B₁₂ is produced solely by fermentation, due to the complexity of its synthesis. *In vitro* methodologies require significant inputs of materials and time, often at great cost.

20 C. Purine, Pyrimidine, Nucleoside and Nucleotide Metabolism and Uses

Purine and pyrimidine metabolism genes and their corresponding proteins are important targets for the therapy of tumor diseases and viral infections. The language "purine" or "pyrimidine" includes the nitrogenous bases which are constituents of nucleic acids, co-enzymes, and nucleotides. The term "nucleotide" includes the basic structural units of nucleic acid molecules, which are comprised of a nitrogenous base, a pentose sugar (in the case of RNA, the sugar is ribose; in the case of DNA, the sugar is D-deoxyribose), and phosphoric acid. The language "nucleoside" includes molecules which serve as precursors to nucleotides, but which are lacking the phosphoric acid moiety that nucleotides possess. By inhibiting the biosynthesis of these molecules, or their mobilization to form nucleic acid molecules, it is possible to inhibit RNA and DNA synthesis; by inhibiting this activity in a fashion targeted to cancerous cells, the ability of tumor cells to divide and replicate may be inhibited. Additionally, there are

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nucleotides which do not form nucleic acid molecules, but rather serve as energy stores (i.e., AMP) or as coenzymes (i.e., FAD and NAD).

Several publications have described the use of these chemicals for these medical indications, by influencing purine and/or pyrimidine metabolism (e.g. Christopherson, R.I. and Lyons, S.D. (1990) "Potent inhibitors of de novo pyrimidine and purine biosynthesis as chemotherapeutic agents." Med. Res. Reviews 10: 505-548). Studies of enzymes involved in purine and pyrimidine metabolism have been focused on the development of new drugs which can be used, for example, as immunosuppressants or anti-proliferants (Smith, J.L., (1995) "Enzymes in nucleotide synthesis." Curr. Opin. Struct. Biol. 5: 752-757; (1995) Biochem Soc. Transact. 23: 877-902). However, purine 10 and pyrimidine bases, nucleosides and nucleotides have other utilities: as intermediates in the biosynthesis of several fine chemicals (e.g., thiamine, S-adenosyl-methionine, folates, or riboflavin), as energy carriers for the cell (e.g., ATP or GTP), and for chemicals themselves, commonly used as flavor enhancers (e.g., IMP or GMP) or for several medicinal applications (see, for example, Kuninaka, A. (1996) Nucleotides and 15 Related Compounds in Biotechnology vol. 6, Rehm et al., eds. VCH: Weinheim, p. 561-612). Also, enzymes involved in purine, pyrimidine, nucleoside, or nucleotide metabolism are increasingly serving as targets against which chemicals for crop protection, including fungicides, herbicides and insecticides, are developed.

The metabolism of these compounds in bacteria has been characterized (for reviews see, for example, Zalkin, H. and Dixon, J.E. (1992) "de novo purine nucleotide biosynthesis", in: Progress in Nucleic Acid Research and Molecular Biology, vol. 42, Academic Press:, p. 259-287; and Michal, G. (1999) "Nucleotides and Nucleosides", Chapter 8 in: Biochemical Pathways: An Atlas of Biochemistry and Molecular Biology, Wiley: New York). Purine metabolism has been the subject of intensive research, and is essential to the normal functioning of the cell. Impaired purine metabolism in higher animals can cause severe disease, such as gout. Purine nucleotides are synthesized from ribose-5-phosphate, in a series of steps through the intermediate compound inosine-5'-phosphate (IMP), resulting in the production of guanosine-5'-monophosphate (GMP) or adenosine-5'-monophosphate (AMP), from which the triphosphate forms utilized as nucleotides are readily formed. These compounds are also utilized as energy stores, so their degradation provides energy for many different biochemical processes in the cell.

Pyrimidine biosynthesis proceeds by the formation of uridine-5'-monophosphate (UMP) from ribose-5-phosphate. UMP, in turn, is converted to cytidine-5'-triphosphate (CTP). The deoxy- forms of all of these nucleotides are produced in a one step reduction reaction from the diphosphate ribose form of the nucleotide to the diphosphate deoxyribose form of the nucleotide. Upon phosphorylation, these molecules are able to participate in DNA synthesis.

D. Trehalose Metabolism and Uses

Trehalose consists of two glucose molecules, bound in α, α-1,1 linkage. It is commonly used in the food industry as a sweetener, an additive for dried or frozen foods, and in beverages. However, it also has applications in the pharmaceutical, cosmetics and biotechnology industries (see, for example, Nishimoto et al., (1998) U.S. Patent No. 5,759,610; Singer, M.A. and Lindquist, S. (1998) Trends Biotech. 16: 460-467; Paiva, C.L.A. and Panek, A.D. (1996) Biotech. Ann. Rev. 2: 293-314; and Shiosaka, M. (1997) J. Japan 172: 97-102). Trehalose is produced by enzymes from many microorganisms and is naturally released into the surrounding medium, from which it can be collected using methods known in the art.

II. Resistance to Damage from Chemicals, Environmental Stress, and Antibiotics

Production of fine chemicals is typically performed by large-scale culture of bacteria developed to produce and secrete large quantities of these molecules. However, this type of large-scale fermentation results in the subjection of the microorganisms to stresses of various kinds. These stresses include environmental stress and chemical stress.

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A. Resistance to Environmental Stress

Examples of environmental stresses typically encountered in large-scale fermentative culture include mechanical stress, heat stress, stress due to limited oxygen, stress due to oxygen radicals, pH stress, and osmotic stress. The stirring mechanism used in most large-scale fermentors to ensure aeration of the culture produces heat, thus increasing the temperature of the culture. Increases in temperature induce the well-characterized heat shock response, in which a set of proteins are expressed which not

only aid in the survival of the bacterium in the face of high temperatures, but also increase survival in response to a number of other environmental stresses (see Neidhardt, F.C., et al., eds. (1996) E. coli and Salmonella. ASM Press: Washington, D.C., p. 1382-1399; Wosten, M. M. (1998) FEMS Microbiology Reviews 22(3): 127-50; Bahl, H. et al. (1995) FEMS Microbiology Reviews 17(3): 341-348; Zimmerman, J.L., Cohill, P.R. (1991) New Biologist 3(7): 641-650; Samali, A., and Orrenius, S. (1998) Cell. Stress Chaperones 3(4): 228-236, and references contained therein from each of these citations). Regulation of the heat shock response in bacteria is facilitated by specific sigma factors and other cellular regulators of gene expression (Hecker, M., Volker, U (1998). Molecular Microbiology 29(5): 1129-1136). One of the largest 10 problems that the cell encounters when exposed to high temperature is that protein folding is impaired; nascent proteins have sufficient kinetic energy in high temperature circumstances that it is difficult for the growing polypeptide chain to remain in a stable conformation long enough to fold properly. Thus, two of the key types of proteins expressed during the heat shock response consist of chaperones (proteins which assist in 15 the folding or unfolding of other proteins - see, e.g., Fink, A.L. (1999) Physiol. Rev. 79(2): 425-449), and proteases, which can destroy any improperly folded proteins. Examples of chaperones expressed during the heat shock response include GroEL and DNAK; proteases known to be expressed during this cellular reaction to heat shock include Lon, FtsH, and ClpB. 20

Other environmental stresses besides heat may also provoke a stress response. Though the fermentor stirring process is meant to introduce oxygen into the culture, oxygen may remain in limited supply, particularly when the culture is advanced in growth and the oxygen needs of the culture are thereby increased; an insufficient supply of oxygen is another stress for the microorganism. Cells in fermentor cultures are also subjected to a number of osmotic stresses, particularly when nutrients are added to the culture, resulting in a high extracellular and low intracellular concentration of these molecules. Further, the large quantities of the desired molecules produced by these organisms in culture may contribute to osmotic stress of the bacteria. Lastly, aerobic metabolism such as that used by *C. glutamicum* results in carbon dioxide as a waste product; secretion of this molecule may acidify the culture medium due to conversion of this molecule to carboxylic acid. Thus, bacteria in culture are also frequently subjected

to acidic pH stress. The converse may also be true—when high levels of basic waste molecules such as ammonium are present in the culture medium, the bacteria in culture may be subjected to basic pH stress as well.

To combat such environmental stresses, bacteria have elegant gene systems which are expressed upon exposure to one or more stresses, such as the aforementioned heat shock system. Genes expressed in response to osmotic stress, for example, encode proteins capable of transporting or synthesizing compatible solutes such that osmotic intake or export of a particular molecule is slowed to manageable levels. Other examples of stress-induced bacterial proteins are those involved in trehalose biosynthesis, those encoding enzymes involved in ppGpp metabolism, those involved in signal transduction, particularly those encoding two-component systems which are sensitive to osmotic pressure, and those encoding transcription factors which are responsive to a variety of stress factors (e.g., RssB analogues and/or sigma factors). Many other such genes and their protein products are known in the art.

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B. Resistance to Chemical Stress

Aside from environmental stresses, cells may also experience a number of chemical stresses. These may fall into two categories. The first are natural wasteproducts of metabolism and other cellular processes which are secreted by the cell to the surrounding medium. The second are chemicals present in the extracellular medium which do not originate from the cell. Generally, when cells excrete toxic waste products from the concentrated intracellular cytoplasm into the relatively much more dilute extracellular medium, these products dissipate such that extracellular levels of the possibly toxic compound are quite low. However, in large-scale fermentative culture of the bacterium, this may not be the case: so many bacteria are grown in a relatively small environment and at such a high metabolic rate that waste products may accumulate in the medium to nearly toxic levels. Examples of such wastes are carbon dioxide, metal ions, and reactive oxygen species such as hydrogen peroxide. These compounds may interfere with the activity or structure of cell surface molecules, or may re-enter the cell, where they can seriously damage proteins and nucleic acids alike. Certain other chemicals hazardous to the normal functioning of cells may be naturally found in the extracellular medium. For example, metal ions such as mercury, cadmium, nickel or

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copper are frequently found in water sources, and may form tight complexes with cellular enzymes which prevent the normal functioning of these proteins.

C. Resistance to Antibiotics

Bacteriocidal proteins or antibiotics, may also be found in the extracellular milieu, either through the intervention of the researcher, or as a natural product from another organism, utilized to gain a competitive advantage. Microorganisms have several art-known mechanisms to protect themselves against antimicrobial chemicals. Degradation, modification, and export of compounds toxic to the cell are common methods by which microorganisms eliminate or detoxify antibiotics. Cytoplasmic 'efflux-pumps' are known in several prokaryotes and show similarities to the so-called 'multidrug resistance' proteins from higher eukaryotes (Neyfakh, A. A., et al. (1991) Proc. Natl. Acad. Sci. USA 88: 4781-4785). Examples of such proteins include emrAB from E. coli (Lomovskaya, O. and K. Lewis (1992) Proc. Natl. Acad. Sci. USA 89: 8938-8942), lmrB from B. subtilis (Kumano, M. et al. (1997) Microbiology 143: 2775-2782), smr from S. aureus (Grinius, L.G. et al. (1992) Plasmid 27: 119-129) or cmr from C. glutamicum (Kaidoh, K. et al. (1997) Micro. Drug Resist. 3: 345-350). .C. glutamicum itself is non-pathogenic, in contrast to several other members of the genus Corynebacterium, such as C. diphtheriae or C. pseudotuberculosis. Several pathogenic Corynebacteria are known to have multiple resistances against a variety of antibiotics, such as C. jeikeium and C. urealyticum (Soriano, F. et al. (1995) Antimicrob. Agents Chemother. 39: 208-214).

Lincosamides are recognized as effective antibiotics against Corynebacterium species (Soriano, F. et al. (1995) Antimicrob. Agents Chemother. 39: 208-214). An unexpected result of the present invention was the identification of a gene encoding a lincosamide-resistance protein (in particular, a lincomycin-resistance protein). The LMRB protein from C. glutamicum shows 40% homology to the product of the lmrB gene from B. subtilis (see Genbank accession no. AL009126), as calculated using version 1.7 of the program CLUSTALW (Thompson, J.D., Higgins, D.G., Gibson, T. J. (1994) Nucl. Acids Res. 22: 4673-4680) using standard parameters (PAIRWISE ALIGNMENT PARAMETERS: slow/accurate alignments: Gap Open Penalty = 10.00, Gap Extension Penalty = 0.10, Protein weight matrix = BLOSUM 30, DNA weight

matrix = IUB, Fast/Approximate alignments: Gap penalty = 3, K-tuple (word) size = 1, No. of top diagonals = 5, Window size = 5, Toggle Slow/Fast pairwise alignments = slow. Multiple alignment parameters: Gap Opening Penalty = 10.00, Gap Extension Penalty = 0.05, Delay divergent sequences = 40%, DNA transitions weight = 0.50, Protein weight matrix = BLOSUM series, DNA weight matrix = IUB, Use negative matrix = OFF).

Environmental stress, chemical stress, and antibiotic or other antimicrobial stress may influence the behavior of the microorganisms during fermentor culture, and may have an impact on the production of the desired compound from these organisms. For example, osmotic stress of a microorganism may cause inappropriate or inappropriately rapid uptake of one or more compounds which can ultimately lead to cellular damage or death due to osmotic shock. Similarly, chemicals present in the culture, either exogenously added (e.g., antimicrobial compounds intended to eliminate unwanted microbes) or generated by the bacteria themselves (e.g., waste compounds such as heavy metals or oxygen radicals, or even antimicrobial compounds) may result in inhibition of fine chemical production or even death of the organism. The genes of the invention encode C. glutamicum proteins which act to prevent cell damage or death, by specifically counteracting the source or effect of the environmental or chemical stress.

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III. Elements and Methods of the Invention

The present invention is based, at least in part, on the discovery of novel molecules, referred to herein as SRT nucleic acid and protein molecules, which increase the ability of *C. glutamicum* to survive in chemically or environmentally hazardous settings. In one embodiment, the SRT molecules function to confer resistance to one or more environmental or chemical stresses to *C. glutamicum*. In a preferred embodiment, the activity of the SRT molecules of the present invention has an impact on the production of a desired fine chemical by this organism. In a particularly preferred embodiment, the SRT molecules of the invention are modulated in activity, such that the yield, production, and/or efficiency of production of one or more fine chemicals from *C. glutamicum* is also modulated.

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The language, "SRT protein" or "SRT polypeptide" includes proteins which participate in the resistance of C. glutamicum to one or more environmental or chemical stresses. Examples of SRT proteins include those encoded by the SRT genes set forth in Table 1 and by the odd-numbered SEQ ID NOs. The terms "SRT gene" or "SRT nucleic acid sequence" include nucleic acid sequences encoding an SRT protein, which consist of a coding region and also corresponding untranslated 5' and 3' sequence regions. Examples of SRT genes include those set forth in Table 1. The terms "production" or "productivity" are art-recognized and include the concentration of the fermentation product (for example, the desired fine chemical) formed within a given time and a given fermentation volume (e.g., kg product per hour per liter). The term "efficiency of production" includes the time required for a particular level of production to be achieved (for example, how long it takes for the cell to attain a particular rate of output of a fine chemical). The term "yield" or "product/carbon yield" is art-recognized and includes the efficiency of the conversion of the carbon source into the product (i.e., fine chemical). This is generally written as, for example, kg product per kg carbon source. By increasing the yield or production of the compound, the quantity of recovered molecules, or of useful recovered molecules of that compound in a given amount of culture over a given amount of time is increased. The terms "biosynthesis" or a "biosynthetic pathway" are art-recognized and include the synthesis of a compound, preferably an organic compound, by a cell from intermediate compounds in what may be a multistep and highly regulated process. The terms "degradation" or a "degradation pathway" are art-recognized and include the breakdown of a compound, preferably an organic compound, by a cell to degradation products (generally speaking, smaller or less complex molecules) in what may be a multistep and highly regulated process. The language "metabolism" is art-recognized and includes the totality of the biochemical reactions that take place in an organism. The metabolism of a particular compound, then, (e.g., the metabolism of an amino acid such as glycine) comprises the overall biosynthetic, modification, and degradation pathways in the cell related to this compound. The terms "resistance" and "tolerance" are art-known and include the ability of a cell to not be affected by exposure to a chemical or an environment which would otherwise be detrimental to the normal functioning of these organisms. The terms "stress" or "hazard" include factors which are detrimental to the normal functioning of

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cells such as *C. glutamicum*. Examples of stresses include "chemical stress", in which a cell is exposed to one or more chemicals which are detrimental to the cell, and "environmental stress" where a cell is exposed to an environmental condition outside of those to which it is adapted. Chemical stresses may be either natural metabolic waste products such as, but not limited to reactive oxygen species or carbon dioxide, or chemicals otherwise present in the environment, including, but not limited to heavy metal ions or bacteriocidal proteins such as antibiotics. Environmental stresses may be, but are not limited to temperatures outside of the normal range, suboptimal oxygen availability, osmotic pressures, or extremes of pH, for example.

In another embodiment, the SRT molecules of the invention are capable of modulating the production of a desired molecule, such as a fine chemical, in a microorganism such as C. glutamicum. Using recombinant genetic techniques, one or more of the SRT proteins of the invention may be manipulated such that its function is modulated. The alteration of activity of stress response, resistance or tolerance genes such that the cell is increased in tolerance to one or more stresses may improve the ability of that cell to grow and multiply in the relatively stressful conditions of largescale fermentor culture. For example, by overexpressing or engineering a heat-shock induced chaperone molecule such that it is optimized in activity, one may increase the ability of the bacterium to correctly fold proteins in the face of nonoptimal temperature conditions. By having fewer misfolded (and possibly misregulated or nonfunctional) proteins, the cell is increased in its ability to function normally in such a culture, which should in turn provide increased viability. This overall increase in number of cells having greater viability and activity in the culture should also result in an increase in the yield, production, and/or efficiency of production of one or more desired fine chemicals, due at least to the relatively greater number of cells producing these chemicals in the culture.

The isolated nucleic acid sequences of the invention are contained within the genome of a Corynebacterium glutamicum strain available through the American Type Culture Collection, given designation ATCC 13032. The nucleotide sequence of the isolated C. glutamicum SRT DNAs and the predicted amino acid sequences of the C. glutamicum SRT proteins are shown the Sequence Listing as odd-numbered SEQ ID NOs and even-numbered SEQ ID NOs, respectively.,.

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Computational analyses were performed which classified and/or identified these nucleotide sequences as sequences which encode chemical and environmental stress, resistance, and tolerance proteins.

The present invention also pertains to proteins which have an amino acid sequence which is substantially homologous to an amino acid sequence of the invention (e.g., the sequence of an even-numbered SEQ ID NO of the Sequence Listing). As used herein, a protein which has an amino acid sequence which is substantially homologous to a selected amino acid sequence is least about 50% homologous to the selected amino acid sequence, e.g., the entire selected amino acid sequence. A protein which has an amino acid sequence which is substantially homologous to a selected amino acid sequence can also be least about 50-60%, preferably at least about 60-70%, and more preferably at least about 70-80%, 80-90%, or 90-95%, and most preferably at least about 96%, 97%, 98%, 99% or more homologous to the selected amino acid sequence. Ranges and identity values intermediate to the above-recited values, (e.g., 75%-80% identical, 85-87% identical, 91-92% identical) are also intended to be encompassed by the present invention. For example, ranges of identity values using a combination of any of the above values recited as upper and/or lower limits are intended to be included.

The SRT proteins or biologically active portions or fragments thereof of the invention can confer resistance or tolerance to one or more chemical or environmental stresses, or may have one or more of the activities set forth in Table 1.

Various aspects of the invention are described in further detail in the following subsections:

A. Isolated Nucleic Acid Molecules

One aspect of the invention pertains to isolated nucleic acid molecules that encode SRT polypeptides or biologically active portions thereof, as well as nucleic acid fragments sufficient for use as hybridization probes or primers for the identification or amplification of SRT-encoding nucleic acid (e.g., SRT DNA). As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (e.g., cDNA or genomic DNA) and RNA molecules (e.g., mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. This term also encompasses untranslated sequence located at both the 3' and 5' ends of the coding region of the gene: at least about 100 nucleotides

of sequence upstream from the 5' end of the coding region and at least about 20 nucleotides of sequence downstream from the 3'end of the coding region of the gene. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA. An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic 5 acid. Preferably, an "isolated" nucleic acid is free of sequences which naturally flank the nucleic acid (i.e., sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated SRT nucleic acid molecule can contain less than about 5 kb, 4kb, 3kb, 2kb, 1 kb, 0.5 kb or 0.1 kb of nucleotide sequences which 10 naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived (e.g, a C. glutamicum cell). Moreover, an "isolated" nucleic acid molecule, such as a DNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the present invention, e.g., a nucleic acid molecule having a nucleotide sequence of an odd-numbered SEQ ID NO of the Sequence Listing, or a portion thereof, can be isolated using standard molecular biology techniques and the sequence information provided herein. For example, a C. glutamicum SRT DNA can be isolated from a C. glutamicum library using all or portion of one of the odd-numbered 20 SEQ ID NO sequences of the Sequence Listing as a hybridization probe and standard hybridization techniques (e.g., as described in Sambrook, J., Fritsh, E. F., and Maniatis, T. Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989). Moreover, a nucleic acid molecule encompassing all or a portion of one of the nucleic 25 acid sequences of the invention (e.g., an odd-numbered SEQ ID NO:) can be isolated by the polymerase chain reaction using oligonucleotide primers designed based upon this sequence (e.g., a nucleic acid molecule encompassing all or a portion of one of the nucleic acid sequences of the invention (e.g., an odd-numbered SEQ ID NO of the Sequence Listing) can be isolated by the polymerase chain reaction using 30 oligonucleotide primers designed based upon this same sequence). For example, mRNA can be isolated from normal endothelial cells (e.g., by the guanidinium-thiocyanate

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extraction procedure of Chirgwin et al. (1979) Biochemistry 18: 5294-5299) and DNA can be prepared using reverse transcriptase (e.g., Moloney MLV reverse transcriptase, available from Gibco/BRL, Bethesda, MD; or AMV reverse transcriptase, available from Seikagaku America, Inc., St. Petersburg, FL). Synthetic oligonucleotide primers for polymerase chain reaction amplification can be designed based upon one of the nucleotide sequences shown in the Sequence Listing. A nucleic acid of the invention can be amplified using cDNA or, alternatively, genomic DNA, as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, oligonucleotides corresponding to an SRT nucleotide sequence can be prepared by standard synthetic techniques, e.g., using an automated DNA synthesizer.

In a preferred embodiment, an isolated nucleic acid molecule of the invention comprises one of the nucleotide sequences shown in the Sequence Listing. The nucleic acid sequences of the invention, as set forth in the Sequence Listing, correspond to the Corynebacterium glutamicum SRT DNAs of the invention. This DNA comprises sequences encoding SRT proteins (i.e., the "coding region", indicated in each oddnumbered SEQ ID NO: sequence in the Sequence Listing), as well as 5' untranslated sequences and 3' untranslated sequences, also indicated in each odd-numbered SEQ ID NO: in the Sequence Listing. Alternatively, the nucleic acid molecule can comprise only the coding region of any of the nucleic acid sequences of the Sequence Listing.

For the purposes of this application, it will be understood that each of the nucleic acid and amino acid sequences set forth in the Sequence Listing has an identifying RXA, RXN, or RXS number having the designation "RXA", "RXN", or "RXS" followed by 5 digits (i.e., RXA01524, RXN00493, or RXS01027). Each of the nucleic acid sequences 25 comprises up to three parts: a 5' upstream region, a coding region, and a downstream region. Each of these three regions is identified by the same RXA, RXN, or RXS designation to eliminate confusion. The recitation "one of the odd-numbered sequences of the Sequence Listing", then, refers to any of the nucleic acid sequences in the Sequence Listing, , which may be also be distinguished by their differing RXA, RXN, or RXS designations. The coding region of each of these sequences is translated into a corresponding amino acid sequence, which is also et forth in the Sequence Listing, as an

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even-numbered SEQ ID NO: immediately following the corresponding nucleic acid sequence. For example, the coding region for RXA01524 is set forth in SEQ ID NO:1, while the amino acid sequence which it encodes is set forth as SEQ ID NO:2. The sequences of the nucleic acid molecules of the invention are identified by the same RXA, RXN, or RXS designations as the amino acid molecules which they encode, such that they can be readily correlated. For example, the amino acid sequence designated RXA01524 is a translation of the coding region of the nucleotide sequence of nucleic acid molecule RXA01524, the amino acid sequence designated RXN00034 is a translation of the coding region of the nucleotide sequence of nucleic acid molecule RXN00034, and the amino acid sequence in designated RXS00568 is a translation of the coding region of the nucleotide sequence of nucleic acid molecule RXS00568. The correspondence between the RXA, RXN, and RXS nucleotide and amino acid sequences of the invention and their assigned SEQ ID NOs is set forth in Table 1.

Several of the genes of the invention are "F-designated genes". An F-designated gene includes those genes set forth in Table 1 which have an 'F' in front of the RXA, RXN, or RXS designation. For example, SEQ ID NO:7, designated, as indicated on Table 1, as "F RXA00498", is an F-designated gene, as are SEQ ID NOs: 25, 33, and 37 (designated on Table 1 as "F RXA01345", "F RXA02543", and "F RXA02282", respectively).

In one embodiment, the nucleic acid molecules of the present invention are not intended to include those compiled in Table 2. In the case of the dapD gene, a sequence for this gene was published in Wehrmann, A., et al. (1998) J. Bacteriol. 180(12): 3159-3165. However, the sequence obtained by the inventors of the present application is significantly longer than the published version. It is believed that the published version relied on an incorrect start codon, and thus represents only a fragment of the actual coding region.

In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which is a complement of one of the nucleotide sequences of the invention (e.g., a sequence of an odd-numbered SEQ ID NO: of the Sequence Listing, or a portion thereof. A nucleic acid molecule which is complementary to one of the nucleotide sequences of the invention is one which is sufficiently complementary to one of the nucleotide sequences shown in the Sequence

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Listing (e.g., the sequence of an odd-numbered SEQ ID NO:) such that it can hybridize to one of the nucleotide sequences of the invention, thereby forming a stable duplex.

In still another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleotide sequence which is at least about 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60%, preferably at least about 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, or 70%%, more preferably at least about 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, or 90%, or 91%, 92%, 93%, 94%, and even more preferably at least about 95%, 96%, 97%, 98%, 99% or more homologous to a nucleotide sequence of the invention (e.g., a sequence of an odd-numbered SEQ ID NO: of the Sequence Listing), or a portion thereof. Ranges and identity values intermediate to the above-recited ranges, (e.g., 70-90% identical or 80-95% identical) are also intended to be encompassed by the present invention. For example, ranges of identity values using a combination of any of the above values recited as upper and/or lower limits are intended to be included. In an additional preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleotide sequence which hybridizes, e.g., hybridizes under stringent conditions, to one of the nucleotide sequences of the invention, or a portion thereof.

Moreover, the nucleic acid molecule of the invention can comprise only a portion of the coding region of the sequence of one of the odd-numbered SEQ ID NOs of the Sequence Listing for example a fragment which can be used as a probe or primer or a fragment encoding a biologically active portion of an SRT protein. The nucleotide sequences determined from the cloning of the SRT genes from *C. glutamicum* allows for the generation of probes and primers designed for use in identifying and/or cloning SRT homologues in other cell types and organisms, as well as SRT homologues from other *Corynebacteria* or related species. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, preferably about 25, more preferably about 40, 50 or 75 consecutive nucleotides of a sense strand of one of the nucleotide sequences of the invention (e.g., a sequence of one of the odd-numbered SEQ ID NOs of the Sequence Listing),, an anti-cense sequence of one of these

Prime. 4 on a nucleotide anver an can sed in Tar reactions to other SRT homologues.

Probes based on the SRT nucleotide sequences can-be used to detect transcripts or genomic sequences encoding the same or homologous proteins. In preferred embodiments, the probe further comprises a label group attached thereto, e.g. the label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme cofactor. Such probes can be used as a part of a diagnostic test kit for identifying cells which misexpress an SRT protein, such as by measuring a level of an SRT-encoding nucleic acid in a sample of cells, e.g., detecting SRT mRNA levels or determining whether a genomic SRT gene has been mutated or deleted.

In one embodiment, the nucleic acid molecule of the invention encodes a protein or portion thereof which includes an amino acid sequence which is sufficiently 10 homologous to an amino acid sequence of the invention (e.g., a sequence of an evennumbered SEQ ID NO of the Sequence Listing) such that the protein or portion thereof maintains the ability to confer resistance or tolerance of C. glutamicum to one or more chemical or environmental stresses. As used herein, the language "sufficiently homologous" refers to proteins or portions thereof which have amino acid sequences 15 which include a minimum number of identical or equivalent (e.g., an amino acid residue which has a similar side chain as an amino acid residue in a sequence of one of the evennumbered SEQ ID NOs of the Sequence Listing) amino acid residues to an amino acid sequence of the invention such that the protein or portion thereof is capable of participating in the resistance of C. glutamicum to one or more chemical or 20 environmental stresses. Protein members of such metabolic pathways, as described herein, function to increase the resistance or tolerance of C. glutamicum to one or more environmental or chemical hazards or stresses. Examples of such activities are also described herein. Thus, "the function of an SRT protein" contributes to the overall resistance of C. glutamicum to elements of its sec 25 which may impede its normal growth or functioning, and/or contributes, either dia ctly, to the yield, production, and/or efficiency of production of one or more micals. Examples of SRT protein activities are set forth a lable 1.

In another embodiment, the protein is at leas. Out 50-60%, preferably at least about 60-70%, and more preferably at least about 70-100%, 90-95%, and most preferably at least about 96%, 97%, 98%, 99% or entire amino acid sequence of the invention (e.g., a sequence of an even-numbered SEQ ID NO: of

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the Sequence Listing). Ranges and identity values intermediate to the above-recited values, (e.g., 75%-80% identical, 85-87% identical, or 91-92% identical) are also intended to be encompassed by the present invention. For example, ranges of identity values using a combination of any of the above values recited as upper and/or lower limits are intended to be included.

Portions of proteins encoded by the SRT nucleic acid molecules of the invention are preferably biologically active portions of one of the SRT proteins. As used herein, the term "biologically active portion of an SRT protein" is intended to include a portion, e.g., a domain/motif, of an SRT protein that is capable of imparting resistance or tolerance to one or more environmental or chemical stresses or hazards, or has an activity as set forth in Table 1. To determine whether an SRT protein or a biologically active portion thereof can increase the resistance or tolerance of C. glutamicum to one or more chemical or environmental stresses or hazards, an assay of enzymatic activity may be performed. Such assay methods are well known to those of ordinary skill in the art, as detailed in Example 8 of the Exemplification.

Additional nucleic acid fragments encoding biologically active portions of an SRT protein can be prepared by isolating a portion of one of the amino acid sequences of the invention (e.g., a sequence of an even-numbered SEQ ID NO: of the Sequence Listing), expressing the encoded portion of the SRT protein or peptide (e.g., by recombinant expression in vitro) and assessing the activity of the encoded portion of the SRT protein or peptide.

The invention further encompasses nucleic acid molecules that differ from one of the nucleotide sequences of the invention (e.g., a sequence of an odd-numbered SEQ ID NO: of the Sequence Listing) (and portions thereof) due to degeneracy of the genetic code and thus encode the same SRT protein as that encoded by the nucleotide sequences of the invention. In another embodiment, an isolated nucleic acid molecule of the invention has a nucleotide sequence encoding a protein having an amino acid sequence shown in the Sequence Listing (e.g., an even-numbered SEQ ID NO:).. In a still further embodiment, the nucleic acid molecule of the invention encodes a full length C. glutamicum protein which is substantially homologous to an amino acid sequence of the invention (encoded by an open reading frame shown in an odd-numbered SEQ ID NO: of the Sequence Listing).

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It will be understood by one of ordinary skill in the art that in one embodiment the sequences of the invention are not meant to include the sequences of the prior art, such as those Genbank sequences set forth in Tables 2 or 4 which were available prior to the present invention. In one embodiment, the invention includes nucleotide and amino acid sequences having a percent identity to a nucleotide or amino acid sequence of the invention which is greater than that of a sequence of the prior art (e.g., a Genbank sequence (or the protein encoded by such a sequence) set forth in Tables 2 or 4). For example, the invention includes a nucleotide sequence which is greater than and/or at least 39% identical to the nucleotide sequence designated RXA00084 (SEQ ID NO:189), a nucleotide sequence which is greater than and/or at least 56% identical to the nucleotide sequence designated RXA00605 (SEQ ID NO:11), and a nucleotide sequence which is greater than and/or at least 50% identical to the nucleotide sequence designated RXA00886 (SEQ ID NO:39). One of ordinary skill in the art would be able to calculate the lower threshold of percent identity for any given sequence of the invention by examining the GAP-calculated percent identity scores set forth in Table 4 for each of the three top hits for the given sequence, and by subtracting the highest GAP-calculated percent identity from 100 percent. One of ordinary skill in the art will also appreciate that nucleic acid and amino acid sequences having percent identities greater than the lower threshold so calculated (e.g., at least 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60%, preferably at least about 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, or 70%, more preferably at least about 71%, 72%, 73%, 74%, 75%,

67%, 68%, 69%, or 70%, more preferably at least about 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, or 90%, or 91%, 92%, 93%, 94%, and even more preferably at least about 95%, 96%, 97%, 98%, 99% or more identical) are also encompassed by the invention.

In addition to the *C. glutamicum* SRT nucleotide sequences set forth in the

In addition to the *C. glutamicum* SRT nucleotide sequences set forth in the Sequence Listing as odd-numbered SEQ ID NOs, it will be appreciated by one of ordinary skill in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of SRT proteins may exist within a population (*e.g.*, the *C. glutamicum* population). Such genetic polymorphism in the SRT gene may exist among individuals within a population due to natural variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding an SRT protein, preferably a *C. glutamicum* SRT protein. Such

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natural variations can typically result in 1-5% variance in the nucleotide sequence of the SRT gene. Any and all such nucleotide variations and resulting amino acid polymorphisms in SRT that are the result of natural variation and that do not alter the functional activity of SRT proteins are intended to be within the scope of the invention.

Nucleic acid molecules corresponding to natural variants and non-C. glutamicum homologues of the C. glutamicum SRT DNA of the invention can be isolated based on their homology to the C. glutamicum SRT nucleic acid disclosed herein using the C. glutamicum DNA, or a portion thereof, as a hybridization probe according to standard hybridization techniques under stringent hybridization conditions. Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 15 nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising a nucleotide sequence of an odd-numbered SEQ ID NO: of the Sequence Listing. In other embodiments, the nucleic acid is at least 30, 50, 100, 250 or more nucleotides in length. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% homologous to each other typically remain hybridized to each other. Preferably, the conditions are such that sequences at least about 65%, more preferably at least about 70%, and even more preferably at least about 75% or more homologous to each other typically remain hybridized to each other. Such stringent conditions are known to those of ordinary skill in the art in the art and can be found in Ausubel et al., Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50-65°C. Preferably, an isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to a nucleotide sequence of the invention corresponds to a naturally-occurring nucleic acid molecule. As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (e.g., encodes a natural protein). In one embodiment, the nucleic acid encodes a natural C. glutamicum SRT protein.

In addition to naturally-occurring variants of the SRT sequence that may exist in the population, one of ordinary skill in the art will further appreciate that changes can be

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introduced by mutation into a nucleotide sequence of the invention, thereby leading to changes in the amino acid sequence of the encoded SRT protein, without altering the functional ability of the SRT protein. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in a nucleotide sequence of the invention. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of one of the SRT proteins (e.g., an even-numbered SEQ ID NO: of the Sequence Listing) without altering the activity of said SRT protein, whereas an "essential" amino acid residue is required for SRT protein activity. Other amino acid residues, however, (e.g., those that are not conserved or only semi-conserved in the domain having SRT activity) may not be essential for activity and thus are likely to be amenable to alteration without altering SRT activity.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding SRT proteins that contain changes in amino acid residues that are not essential for SRT activity. Such SRT proteins differ in amino acid sequence from a sequence of an even-numbered SEQ ID NO: of the Sequence Listing yet retain at least one of the 15 SRT activities described herein. In one embodiment, the isolated nucleic acid molecule comprises a nucleotide sequence encoding a protein, wherein the protein comprises an amino acid sequence at least about 50% homologous to an amino acid sequence of the invention and is capable of increasing the resistance or tolerance of C. glutamicum to one or more environmental or chemical stresses, or has one or more of the activities set 20 forth in Table 1. Preferably, the protein encoded by the nucleic acid molecule is at least about 50-60% homologous to the amino acid sequence of one of the odd-numbered SEQ ID NOs of the Sequence Listing, more preferably at least about 60-70% homologous to one of these sequences, even more preferably at least about 70-80%, 80-90%, 90-95% homologous to one of these sequences in, and most preferably at least about 96%, 97%, 98%, or 99% homologous to one of the amino acid sequences of the invention.

To determine the percent homology of two amino acid sequences (e.g., one of the amino acid sequences of the invention and a mutant form thereof) or of two nucleic acids, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of one protein or nucleic acid for optimal alignment with the other protein or nucleic acid). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in one

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sequence (e.g., one of the amino acid sequences of the invention) is occupied by the same amino acid residue or nucleotide as the corresponding position in the other sequence (e.g., a mutant form of the amino acid sequence), then the molecules are homologous at that position (i.e., as used herein amino acid or nucleic acid "homology" is equivalent to amino acid or nucleic acid "identity"). The percent homology between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % homology = # of identical positions/total # of positions x 100).

An isolated nucleic acid molecule encoding an SRT protein homologous to a protein sequence of the invention (e.g., a sequence of an even-numbered SEQ ID NO: of the Sequence Listing)can be created by introducing one or more nucleotide 10 substitutions, additions or deletions into a nucleotide sequence of the invention such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein. Mutations can be introduced into one of the nucleotide sequences of the invention by standard techniques, such as site-directed mutagenesis and PCRmediated mutagenesis. Preferably, conservative amino acid substitutions are made at 15 one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic 20 acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue 25 in an SRT protein is preferably replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of an SRT coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for an SRT activity described herein to identify mutants that retain SRT activity. Following mutagenesis of one the nucleotide sequence of one of the odd-numbered SEQ ID NOs of the Sequence Listing, the encoded protein can be expressed recombinantly and the activity of the protein can

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be determined using, for example, assays described herein (see Example 8 of the Exemplification).

In addition to the nucleic acid molecules encoding SRT proteins described above, another aspect of the invention pertains to isolated nucleic acid molecules which are antisense thereto. An "antisense" nucleic acid comprises a nucleotide sequence 5 which is complementary to a "sense" nucleic acid encoding a protein, e.g., complementary to the coding strand of a double-stranded DNA molecule or complementary to an mRNA sequence. Accordingly, an antisense nucleic acid can hydrogen bond to a sense nucleic acid. The antisense nucleic acid can be complementary to an entire SRT coding strand, or to only a portion thereof. In one 10 embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence encoding an SRT protein. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues (e.g., the entire coding region of SEQ ID NO.: 120 (RXA00600) comprises nucleotides 1 to 1098). In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence encoding SRT. The term "noncoding region" refers to 5' and 3' sequences which flank the coding region that are not translated into amino acids (i.e., also referred to as 5' and 3' untranslated regions).

Given the coding strand sequences encoding SRT disclosed herein (e.g., the sequences set forth as odd-numbered SEQ ID NOs in the Sequence Listing), antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of SRT mRNA, but more preferably is an oligonucleotide which is antisense to only a portion of the coding or noncoding region of SRT mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of SRT mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to

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increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-

fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylguanine, 2,2-dimethylguanine, 2-methylguanine, 2-methylguanine, 3-methylcytosine, 5-

methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a cell or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding an SRT protein to thereby inhibit expression of the protein, e.g., by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. The antisense molecule can be modified such that it specifically binds to a receptor or an antigen expressed on a selected cell surface, e.g., by linking the antisense nucleic acid molecule to a peptide or an antibody which binds to a cell surface receptor or antigen. The antisense nucleic acid molecule can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in

which the antisense nucleic acid molecule is placed under the control of a strong prokaryotic, viral, or eukaryotic promoter are preferred.

In yet another embodiment, the antisense nucleic acid molecule of the invention is an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gaultier et al. (1987) Nucleic Acids. Res. 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue et al. (1987) Nucleic Acids Res. 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue et al. (1987) FEBS Lett. 215:327-330).

10 In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (e.g., hammerhead ribozymes (described in Haselhoff and Gerlach (1988) Nature 334:585-591)) can be used to catalytically cleave SRT mRNA transcripts to thereby inhibit translation of SRT mRNA. 15 A ribozyme having specificity for an SRT-encoding nucleic acid can be designed based upon the nucleotide sequence of an SRT cDNA disclosed herein (i.e., SEQ ID NO:119 (RXA00600)). For example, a derivative of a Tetrahymena L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in an SRT-encoding mRNA. See, e.g., Cech et al. 20 U.S. Patent No. 4,987,071 and Cech et al. U.S. Patent No. 5,116,742. Alternatively, SRT mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, e.g., Bartel, D. and Szostak, J.W. (1993) Science 261:1411-1418.

Alternatively, SRT gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region of an SRT nucleotide sequence (e.g., an SRT promoter and/or enhancers) to form triple helical structures that prevent transcription of an SRT gene in target cells. See generally, Helene, C. (1991)

Anticancer Drug Des. 6(6):569-84; Helene, C. et al. (1992) Ann. N.Y. Acad. Sci. 660:27-30 36; and Maher, L.J. (1992) Bioassays 14(12):807-15.

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B. Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding an SRT protein (or a portion thereof). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adenoassociated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operatively linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (e.g., in an in vitro transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel; Gene Expression Technology: Methods in Enzymology 185,

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Academic Press, San Diego, CA (1990). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and those which direct expression of the nucleotide sequence only in certain host cells. Preferred regulatory sequences are, for example, promoters such as cos-, tac-, trp-, tet-, trp-tet-, lpp-, lac-, lpp-lac-, lacI^q-, T7-, T5-, T3-, gal-, trc-, ara-, SP6-, arny, SPO2, λ-P_R- or λ P_L, which are used preferably in bacteria. Additional regulatory sequences are, for example, promoters from yeasts and fungi, such as ADC1, MFα, AC, P-60, CYC1, GAPDH, TEF, rp28, ADH, promoters from plants such as CaMV/35S, SSU, OCS, lib4, usp, STLS1, B33, nos or ubiquitin- or phaseolin-promoters. It is also possible to use artificial promoters. It will be appreciated by one of ordinary skill in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (e.g., SRT proteins, mutant forms of SRT proteins, fusion proteins, etc.).

The recombinant expression vectors of the invention can be designed for expression of SRT proteins in prokaryotic or eukaryotic cells. For example, SRT genes can be expressed in bacterial cells such as C. glutamicum, insect cells (using baculovirus expression vectors), yeast and other fungal cells (see Romanos, M.A. et al. (1992) "Foreign gene expression in yeast: a review", Yeast 8: 423-488; van den Hondel, 20 C.A.M.J.J. et al. (1991) "Heterologous gene expression in filamentous fungi" in: More Gene Manipulations in Fungi, J.W. Bennet & L.L. Lasure, eds., p. 396-428: Academic Press: San Diego; and van den Hondel, C.A.M.J.J. & Punt, P.J. (1991) "Gene transfer systems and vector development for filamentous fungi, in: Applied Molecular Genetics of Fungi, Peberdy, J.F. et al., eds., p. 1-28, Cambridge University Press: Cambridge), 25 algae and multicellular plant cells (see Schmidt, R. and Willmitzer, L. (1988) High efficiency Agrobacterium tumefaciens -mediated transformation of Arabidopsis thaliana leaf and cotyledon explants" Plant Cell Rep.: 583-586), or mammalian cells. Suitable host cells are discussed further in Goeddel, Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, CA (1990). Alternatively, the 30 recombinant expression vector can be transcribed and translated in vitro, for example using T7 promoter regulatory sequences and T7 polymerase.

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Expression of proteins in prokaryotes is most often carried out with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase.

Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith, D.B. and Johnson, K.S. (1988) Gene 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein. In one embodiment, the coding sequence of the SRT protein is cloned into a pGEX expression vector to create a vector encoding a fusion protein comprising, from the N-terminus to the C-terminus, GST-thrombin cleavage site-X protein. The fusion protein can be purified by affinity chromatography using glutathione-agarose resin. Recombinant SRT protein unfused to GST can be recovered by cleavage of the fusion protein with thrombin.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann *et al.*, (1988) *Gene* 69:301-315) pLG338, pACYC184, pBR322, pUC18, pUC19, pKC30, pRep4, pHS1, pHS2, pPLc236, pMBL24, pLG200, pUR290, pIN-25 III113-B1, λgt11, pBdCl, and pET 11d (Studier *et al.*, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 60-89; and Pouwels *et al.*, eds. (1985) Cloning Vectors. Elsevier: New York IBSN 0 444 904018). Target gene expression from the pTrc vector relies on host RNA polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a coexpressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident λ prophage harboring a T7

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gn1 gene under the transcriptional control of the lacUV 5 promoter. For transformation of other varieties of bacteria, appropriate vectors may be selected. For example, the plasmids pIJ101, pIJ364, pIJ702 and pIJ361 are known to be useful in transforming Streptomyces, while plasmids pUB110, pC194, or pBD214 are suited for transformation of Bacillus species. Several plasmids of use in the transfer of genetic information into Corynebacterium include pHM1519, pBL1, pSA77, or pAJ667 (Pouwels *et al.*, eds. (1985) Cloning Vectors. Elsevier: New York IBSN 0 444 904018).

One strategy to maximize recombinant protein expression is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, S., Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, California (1990) 119-128). Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in the bacterium chosen for expression, such as C. glutamicum (Wada et al. (1992) Nucleic Acids Res. 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the SRT protein expression vector is a yeast expression vector. Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1 (Baldari, *et al.*, (1987) *Embo J.* 6:229-234), 2 μ, pAG-1, Yep6, Yep13, pEMBLYe23, pMFa (Kurjan and Herskowitz, (1982) *Cell* 30:933-943), pJRY88 (Schultz *et al.*, (1987) *Gene* 54:113-123), and pYES2 (Invitrogen Corporation, San Diego, CA). Vectors and methods for the construction of vectors appropriate for use in other fungi, such as the filamentous fungi, include those detailed in: van den Hondel, C.A.M.J.J. & Punt, P.J. (1991) "Gene transfer systems and vector development for filamentous fungi, in: Applied Molecular Genetics of Fungi, J.F. Peberdy, *et al.*, eds., p. 1-28, Cambridge University Press: Cambridge, and Pouwels *et al.*, eds. (1985) Cloning Vectors. Elsevier: New York (IBSN 0 444 904018).

Alternatively, the SRT proteins of the invention can be expressed in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., Sf 9 cells) include the pAc series (Smith et al. (1983) Mol. Cell Biol. 3:2156-2165) and the pVL series (Lucklow and Summers (1989) Virology 170:31-39).

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In another embodiment, the SRT proteins of the invention may be expressed in unicellular plant cells (such as algae) or in plant cells from higher plants (e.g., the spermatophytes, such as crop plants). Examples of plant expression vectors include those detailed in: Becker, D., Kemper, E., Schell, J. and Masterson, R. (1992) "New plant binary vectors with selectable markers located proximal to the left border", *Plant Mol. Biol.* 20: 1195-1197; and Bevan, M.W. (1984) "Binary *Agrobacterium* vectors for plant transformation", *Nucl. Acid. Res.* 12: 8711-8721, and include pLGV23, pGHlac+, pBIN19, pAK2004, and pDH51 (Pouwels et al., eds. (1985) Cloning Vectors. Elsevier: New York IBSN 0 444 904018).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, B. (1987) Nature 329:840) and pMT2PC (Kaufman et al. (1987) EMBO J. 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements.

15 For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook, J., Fritsh, E. F., and Maniatis, T. Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory, Press, Cold Spring Harbor, NY, 1989.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert et al. (1987) Genes Dev. 1:268-277), lymphoid-specific promoters (Calame and Eaton (1988) Adv. Immunol. 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore (1989) EMBO J. 8:729-733) and immunoglobulins (Banerji et al. (1983) Cell 33:729-740; Queen and Baltimore (1983) Cell 33:741-748), neuron-specific promoters (e.g., the neurofilament promoter; Byrne and Ruddle (1989) PNAS 86:5473-5477), pancreas-specific promoters (Edlund et al. (1985) Science 230:912-916), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Patent No. 4,873,316 and

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European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, for example the murine hox promoters (Kessel and Gruss (1990) Science 249:374-379) and the α -fetoprotein promoter (Campes and Tilghman (1989) Genes Dev. 3:537-546).

The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to SRT mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub, H. et al., Antisense RNA as a molecular tool for genetic analysis, Reviews - Trends in Genetics, Vol. 1(1) 1986.

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, an SRT protein can be expressed in bacterial cells such as *C. glutamicum*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those of ordinary skill in the art. Microorganisms related

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to Corynebacterium glutamicum which may be conveniently used as host cells for the nucleic acid and protein molecules of the invention are set forth in Table 3.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (e.g., linear DNA or RNA (e.g., a linearized vector or a gene construct alone without a vector) or nucleic acid in the form of a vector (e.g., a plasmid, phage, phasmid, phagemid, transposon or other DNA)) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, et al. (Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the
expression vector and transfection technique used, only a small fraction of cells may
integrate the foreign DNA into their genome. In order to identify and select these
integrants, a gene that encodes a selectable marker (e.g., resistance to antibiotics) is
generally introduced into the host cells along with the gene of interest. Preferred
selectable markers include those which confer resistance to drugs, such as G418,
hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be
introduced into a host cell on the same vector as that encoding an SRT protein or can be
introduced on a separate vector. Cells stably transfected with the introduced nucleic
acid can be identified by drug selection (e.g., cells that have incorporated the selectable
marker gene will survive, while the other cells die).

To create a homologous recombinant microorganism, a vector is prepared which contains at least a portion of an SRT gene into which a deletion, addition or substitution has been introduced to thereby alter, e.g., functionally disrupt, the SRT gene.

Preferably, this SRT gene is a Corynebacterium glutamicum SRT gene, but it can be a homologue from a related bacterium or even from a mammalian, yeast, or insect source. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous SRT gene is functionally disrupted (i.e., no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively,

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sRT gene is mutated or otherwise altered but still encodes functional protein (e.g., the upstream regulatory region can be altered to thereby alter the expression of the endogenous SRT protein). In the homologous recombination vector, the altered portion of the SRT gene is flanked at its 5' and 3' ends by additional nucleic acid of the SRT gene to allow for homologous recombination to occur between the exogenous SRT gene carried by the vector and an endogenous SRT gene in a microorganism. The additional flanking SRT nucleic acid is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see e.g., Thomas, K.R., and Capecchi, M.R. (1987) Cell 51: 503 for a description of homologous recombination vectors). The vector is introduced into a microorganism (e.g., by electroporation) and cells in which the introduced SRT gene has homologously recombined with the endogenous SRT gene are selected, using art-known techniques.

In another embodiment, recombinant microorganisms can be produced which contain selected systems which allow for regulated expression of the introduced gene. For example, inclusion of an SRT gene on a vector placing it under control of the lac operon permits expression of the SRT gene only in the presence of IPTG. Such regulatory systems are well known in the art.

In another embodiment, an endogenous SRT gene in a host cell is disrupted (e.g., by homologous recombination or other genetic means known in the art) such that expression of its protein product does not occur. In another embodiment, an endogenous or introduced SRT gene in a host cell has been altered by one or more point mutations, deletions, or inversions, but still encodes a functional SRT protein. In still another embodiment, one or more of the regulatory regions (e.g., a promoter, repressor, or inducer) of an SRT gene in a microorganism has been altered (e.g., by deletion, truncation, inversion, or point mutation) such that the expression of the SRT gene is modulated. One of ordinary skill in the art will appreciate that host cells containing more than one of the described SRT gene and protein modifications may be readily produced using the methods of the invention, and are meant to be included in the present invention.

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (i.e., express) an SRT protein. Accordingly, the invention further provides methods for producing SRT proteins using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding an SRT protein has been introduced, or into which genome has been introduced a gene encoding a wild-type or altered SRT protein) in a suitable medium until SRT protein is produced. In another embodiment, the method further comprises isolating SRT proteins from the medium or the host cell.

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C. Isolated SRT Proteins

Another aspect of the invention pertains to isolated SRT proteins, and biologically active portions thereof. An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of SRT protein in which the protein is separated from cellular components of the cells in which it is naturally or recombinantly produced. In one embodiment, the language "substantially free of cellular material" includes preparations of SRT protein having less than about 30% (by dry weight) of non-SRT protein (also referred to herein as a "contaminating protein"), more preferably less than about 20% of non-SRT protein, still more preferably less than about 10% of non-SRT protein, and most preferably less than about 5% non-SRT protein. When the SRT protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture medium represents less than about 20%, more preferably less than about 10%, and most preferably less than about 5% of the volume of the protein preparation. The language "substantially free of chemical precursors or other chemicals" includes preparations of SRT protein in which the protein is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of SRT protein having less than about 30% (by dry weight) of chemical precursors or non-SRT chemicals, more preferably less than

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about 20% chemical precursors or non-SRT chemicals, still more preferably less than about 10% chemical precursors or non-SRT chemicals, and most preferably less than about 5% chemical precursors or non-SRT chemicals. In preferred embodiments, isolated proteins or biologically active portions thereof lack contaminating proteins from the same organism from which the SRT protein is derived. Typically, such proteins are produced by recombinant expression of, for example, a *C. glutamicum* SRT protein in a microorganism such as *C. glutamicum*.

An isolated SRT protein or a portion thereof of the invention can contribute to the resistance or tolerance of C. glutamicum to one or more chemical or environmental stresses or hazards, or has one or more of the activities set forth in Table 1. In preferred embodiments, the protein or portion thereof comprises an amino acid sequence which is sufficiently homologous to an amino acid sequence of the invention (e.g., a sequence of an even-numbered SEQ ID NO: of the Sequence Listing) such that the protein or portion thereof maintains the ability to mediate the resistance or tolerance of C. glutamicum to one or more chemical or environmental stresses or hazards. The portion of the protein is preferably a biologically active portion as described herein. In another preferred embodiment, an SRT protein of the invention has an amino acid sequence set forth as an even-numbered SEQ ID NO: of the Sequence Listing. In yet another preferred embodiment, the SRT protein has an amino acid sequence which is encoded by a nucleotide sequence which hybridizes, e.g., hybridizes under stringent conditions, to a nucleotide sequence of the invention (e.g., a sequence of an odd-numbered SEQ ID NO: of the Sequence Listing). In still another preferred embodiment, the SRT protein has an amino acid sequence which is encoded by a nucleotide sequence that is at least about 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60%, preferably at least about 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, or 70%, more preferably at least about 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, or 90%, or 91%, 92%, 93%, 94%, and even more preferably at least about 95%, 96%, 97%, 98%, 99% or more homologous to one of the nucleic acid sequences of the invention, or a portion thereof. Ranges and identity values intermediate to the above-recited values, (e.g., 70-90% identical or 80-95% identical) are also intended to be encompassed by the present invention. For example, ranges of identity values using a combination of any of the above values recited as upper

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and/or lower limits are intended to be included. The preferred SRT proteins of the present invention also preferably possess at least one of the SRT activities described herein. For example, a preferred SRT protein of the present invention includes an amino acid sequence encoded by a nucleotide sequence which hybridizes, e.g., hybridizes under stringent conditions, to a nucleotide sequence of the invention, and which can increase the resistance or tolerance of C. glutamicum to one or more environmental or chemical stresses, or which has one or more of the activities set forth in Table 1.

In other embodiments, the SRT protein is substantially homologous to an amino acid sequence of the invention (e.g., a sequence of an even-numbered SEQ ID NO: of the Sequence Listing) and retains the functional activity of the protein of one of the amino acid sequences of the invention yet differs in amino acid sequence due to natural variation or mutagenesis, as described in detail in subsection I above. Accordingly, in another embodiment, the SRT protein is a protein which comprises an amino acid sequence which is at least about 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60%, preferably at least about 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, or 70%, more preferably at least about 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, or 90%, or 91%, 92%, 93%, 94%, and even more preferably at least about 95%, 96%, 97%, 98%, 99% or more homologous to an entire amino acid sequence of the invention and which has at least one of the SRT activities described herein. Ranges and identity values intermediate to the above-recited values, (e.g., 70-90% identical or 80-95% identical) are also intended to be encompassed by the present invention. For example, ranges of identity values using a combination of any of the above values recited as upper and/or lower limits are intended to be included. In another embodiment, the invention pertains to a full length C. glutamicum protein which is substantially homologous to an entire amino acid sequence of the invention.

Biologically active portions of an SRT protein include peptides comprising amino acid sequences derived from the amino acid sequence of an SRT protein, e.g., an amino acid sequence of an even-numbered SEQ ID NO: of the Sequence Listing or the amino acid sequence of a protein homologous to an SRT protein, which include fewer amino acids than a full length SRT protein or the full length protein which is homologous to an SRT protein, and exhibit at least one activity of an SRT protein.

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Typically, biologically active portions (peptides, e.g., peptides which are, for example, 5, 10, 15, 20, 30, 35, 36, 37, 38, 39, 40, 50, 100 or more amino acids in length) comprise a domain or motif with at least one activity of an SRT protein. Moreover, other biologically active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the activities described herein. Preferably, the biologically active portions of an SRT protein include one or more selected domains/motifs or portions thereof having biological activity.

SRT proteins are preferably produced by recombinant DNA techniques. For example, a nucleic acid molecule encoding the protein is cloned into an expression vector (as described above), the expression vector is introduced into a host cell (as described above) and the SRT protein is expressed in the host cell. The SRT protein can then be isolated from the cells by an appropriate purification scheme using standard protein purification techniques. Alternative to recombinant expression, an SRT protein, polypeptide, or peptide can be synthesized chemically using standard peptide synthesis techniques. Moreover, native SRT protein can be isolated from cells (e.g., endothelial cells), for example using an anti-SRT antibody, which can be produced by standard techniques utilizing an SRT protein or fragment thereof of this invention.

The invention also provides SRT chimeric or fusion proteins. As used herein, an SRT "chimeric protein" or "fusion protein" comprises an SRT polypeptide operatively linked to a non-SRT polypeptide. An "SRT polypeptide" refers to a polypeptide having 20 an amino acid sequence corresponding to SRT, whereas a "non-SRT polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein which is not substantially homologous to the SRT protein, e.g., a protein which is different from the SRT protein and which is derived from the same or a different organism. Within the fusion protein, the term "operatively linked" is intended to indicate that the SRT 25 polypeptide and the non-SRT polypeptide are fused in-frame to each other. The non-SRT polypeptide can be fused to the N-terminus or C-terminus of the SRT polypeptide. For example, in one embodiment the fusion protein is a GST-SRT fusion protein in which the SRT sequences are fused to the C-terminus of the GST sequences. Such fusion proteins can facilitate the purification of recombinant SRT proteins. In another 30 embodiment, the fusion protein is an SRT protein containing a heterologous signal sequence at its N-terminus. In certain host cells (e.g., mammalian host cells), expression

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and/or secretion of an SRT protein can be increased through use of a heterologous signal sequence.

Preferably, an SRT chimeric or fusion protein of the invention is produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, for example by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for example, Current Protocols in Molecular Biology, eds. Ausubel et al. John Wiley & Sons: 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST polypeptide). An SRTencoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the SRT protein.

Homologues of the SRT protein can be generated by mutagenesis, e.g., discrete point mutation or truncation of the SRT protein. As used herein, the term "homologue" refers to a variant form of the SRT protein which acts as an agonist or antagonist of the activity of the SRT protein. An agonist of the SRT protein can retain substantially the same, or a subset, of the biological activities of the SRT protein. An antagonist of the SRT protein can inhibit one or more of the activities of the naturally occurring form of the SRT protein, by, for example, competitively binding to a downstream or upstream member of the SRT system which includes the SRT protein. Thus, the C. glutamicum SRT protein and homologues thereof of the present invention may increase the tolerance or resistance of C. glutamicum to one or more chemical or environmental stresses.

In an alternative embodiment, homologues of the SRT protein can be identified by screening combinatorial libraries of mutants, e.g., truncation mutants, of the SRT protein for SRT protein agonist or antagonist activity. In one embodiment, a variegated library of SRT variants is generated by combinatorial mutagenesis at the nucleic acid

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level and is encoded by a variegated gene library. A variegated library of SRT variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential SRT sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (e.g., for phage display) containing the set of SRT sequences therein. There are a variety of methods which can be used to produce libraries of potential SRT homologues from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential SRT sequences. Methods for synthesizing degenerate oligonucleotides are known in the art (see, e.g., Narang, S.A. (1983) Tetrahedron 39:3; Itakura et al. (1984) Annu. Rev. Biochem. 53:323; Itakura et al. (1984) Science 198:1056; Ike et al. (1983) Nucleic Acid Res. 11:477.

In addition, libraries of fragments of the SRT protein coding can be used to generate a variegated population of SRT fragments for screening and subsequent selection of homologues of an SRT protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of an SRT coding sequence with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes N-terminal, C-terminal and internal fragments of various sizes of the SRT protein.

Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of SRT homologues. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of

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vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a new technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify SRT homologues (Arkin and Yourvan (1992) PNAS 89:7811-7815; Delgrave et al. (1993) Protein Engineering 6(3):327-331).

In another embodiment, cell based assays can be exploited to analyze a variegated SRT library, using methods well known in the art.

10 D. Uses and Methods of the Invention

The nucleic acid molecules, proteins, protein homologues, fusion proteins, primers, vectors, and host cells described herein can be used in one or more of the following methods: identification of C. glutamicum and related organisms; mapping of genomes of organisms related to C. glutamicum; identification and localization of C. glutamicum sequences of interest; evolutionary studies; determination of SRT protein regions required for function; modulation of an SRT protein activity; modulation of the activity of an SRT pathway; and modulation of cellular production of a desired compound, such as a fine chemical.

The SRT nucleic acid molecules of the invention have a variety of uses. First, they may be used to identify an organism as being Corynebacterium glutamicum or a 20 close relative thereof. Also, they may be used to identify the presence of C. glutamicum or a relative thereof in a mixed population of microorganisms. The invention provides the nucleic acid sequences of a number of C. glutamicum genes; by probing the extracted genomic DNA of a culture of a unique or mixed population of microorganisms under stringent conditions with a probe spanning a region of a C. glutamicum gene which is unique to this organism, one can ascertain whether this organism is present.

Although Corynebacterium glutamicum itself is nonpathogenic, it is related to pathogenic species, such as Corynebacterium diphtheriae. Corynebacterium diphtheriae is the causative agent of diphtheria, a rapidly developing, acute, febrile infection which involves both local and systemic pathology. In this disease, a local lesion develops in the upper respiratory tract and involves necrotic injury to epithelial cells; the bacilli secrete toxin which is disseminated through this lesion to distal susceptible tissues of the

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body. Degenerative changes brought about by the inhibition of protein synthesis in these tissues, which include heart, muscle, peripheral nerves, adrenals, kidneys, liver and spleen, result in the systemic pathology of the disease. Diphtheria continues to have high incidence in many parts of the world, including Africa, Asia, Eastern Europe and the independent states of the former Soviet Union. An ongoing epidemic of diphtheria in the latter two regions has resulted in at least 5,000 deaths since 1990.

In one embodiment, the invention provides a method of identifying the presence or activity of Cornyebacterium diphtheriae in a subject. This method includes detection of one or more of the nucleic acid or amino acid sequences of the invention (e.g., the sequences set forth as odd-numbered or even-numbered SEQ ID NOs, respectively, in the Sequence Listing) in a subject, thereby detecting the presence or activity of Corynebacterium diphtheriae in the subject. C. glutamicum and C. diphtheriae are related bacteria, and many of the nucleic acid and protein molecules in C. glutamicum are homologous to C. diphtheriae nucleic acid and protein molecules, and can therefore be used to detect C. diphtheriae in a subject.

The nucleic acid and protein molecules of the invention may also serve as markers for specific regions of the genome. This has utility not only in the mapping of the genome, but also for functional studies of *C. glutamicum* proteins. For example, to identify the region of the genome to which a particular *C. glutamicum* DNA-binding protein binds, the *C. glutamicum* genome could be digested, and the fragments incubated with the DNA-binding protein. Those which bind the protein may be additionally probed with the nucleic acid molecules of the invention, preferably with readily detectable labels; binding of such a nucleic acid molecule to the genome fragment enables the localization of the fragment to the genome map of *C. glutamicum*, and, when performed multiple times with different enzymes, facilitates a rapid determination of the nucleic acid sequence to which the protein binds. Further, the nucleic acid molecules of the invention may be sufficiently homologous to the sequences of related species such that these nucleic acid molecules may serve as markers for the construction of a genomic map in related bacteria, such as *Brevibacterium lactofermentum*.

The SRT nucleic acid molecules of the invention are also useful for evolutionary and protein structural studies. The resistance processes in which the molecules of the invention participate are utilized by a wide variety of cells; by comparing the sequences

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of the nucleic acid molecules of the present invention to those encoding similar enzymes from other organisms, the evolutionary relatedness of the organisms can be assessed. Similarly, such a comparison permits an assessment of which regions of the sequence are conserved and which are not, which may aid in determining those regions of the protein which are essential for the functioning of the enzyme. This type of determination is of value for protein engineering studies and may give an indication of what the protein can tolerate in terms of mutagenesis without losing function.

The genes of the invention, e.g., the gene encoding LMRB (SEQ ID NO:1) or other gene of the invention encoding a chemical or environmental resistance or tolerance protein (e.g., resistance against one or more antibiotics), may be used as genetic markers for the genetic transformation of (e.g., the transfer of additional genes into or disruption of preexisting genes of) organisms such as C. glutamicum or other bacterial species. Use of these nucleic acid molecules permits efficient selection of organisms which have incorporated a given transgene cassette (e.g., a plasmid, phage, phasmid, phagemid, transposon, or other nucleic acid element), based on a trait which permits the survival of the organism in an otherwise hostile or toxic environment (e.g., in the presence of an antimicrobial compound). By employing one or more of the genes of the invention as genetic markers, the speed and ease with which organisms having desirable transformed traits (e.g., modulated fine chemical production) are engineered and isolated are improved. While it is advantageous to use the genes of the invention for selection of transformed C. glutamicum and related bacteria, it is possible, as described herein, to use homologs (e.g., homologs from other organisms), allelic variants or fragments of the gene retaining desired activity. Furthermore, 5' and 3' regulatory elements of the genes of the invention may be modified as described herein (e.g., by nucleotide substitution, insertion, deletion, or replacement with a more desirable genetic element) to modulate the transcription of the gene. For example, an LMRB variant in which the nucleotide sequence in the region from -1 to -200 5' to the start codon has been altered to modulate (preferably increase) the transcription and/or translation of LMRB may be employed, as can constructs in which a gene of the invention (e.g., the LMRB gene (SEQ ID NO:1)) is functionally coupled to one or more regulatory signals (e.g., inducer or repressor binding sequences) which can be used for modulating gene expression.

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Similarly, more than one copy of a gene (functional or inactivated) of the invention may be employed.

An additional application of the genes of the invention (e.g., the gene encoding LMRB (SEQ ID NO:1) or other drug- or antibiotic-resistance gene) is in the discovery of new antibiotics which are active against Corynebacteria and/or other bacteria. For example, a gene of the invention may be expressed (or overexpressed) in a suitable host to generate an organism with increased resistance to one or more drugs or antibiotics (in the case of LMRB, lincosamides in particular, especially lincomycin). This type of resistant host can subsequently be used to screen for chemicals with bacteriostatic and/or bacteriocidal activity, such as novel antibiotic compounds. It is possible, in particular, to use the genes of the invention (e.g., the LMRB gene) to identify new antibiotics which are active against those microorganisms which are already resistant to standard antibiotic compounds.

The invention provides methods for screening molecules which modulate the activity of an SRT protein, either by interacting with the protein itself or a substrate or binding partner of the SRT protein, or by modulating the transcription or translation of SRT nucleic acid molecule of the invention. In such methods, a microorganism expressing one or more SRT proteins of the invention is contacted with one or more test compounds, and the effect of each test compound on the activity or level of expression of the SRT protein is assessed.

Manipulation of the SRT nucleic acid molecules of the invention may result in the production of SRT proteins having functional differences from the wild-type SRT proteins. These proteins may be improved in efficiency or activity, may be present in greater numbers in the cell than is usual, or may be decreased in efficiency or activity. The goal of such manipulations is to increase the viability and activity of the cell when the cell is exposed to the environmental and chemical stresses and hazards which frequently accompany large-scale fermentative culture. Thus, by increasing the activity or copy number of a heat-shock-regulated protease, one may increase the ability of the cell to destroy incorrectly folded proteins, which may otherwise interfere with normal cellular functioning (for example, by continuing to bind substrates or cofactors although the protein lacks the activity to act on these molecules appropriately). The same is true for the overexpression or optimization of activity of one or more chaperone molecules

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induced by heat or cold shock. These proteins aid in the correct folding of nascent polypeptide chains, and thus their increased activity or presence should increase the percentage of correctly folded proteins in the cell, which in turn should increase the overall metabolic efficiency and viability of the cells in culture. The overexpression or optimization of the transporter molecules activated by osmotic shock should result in an increased ability on the part of the cell to maintain intracellular homeostasis, thereby increasing the viability of these cells in culture. Similarly, the overproduction or increase in activity by mutagenesis of proteins involved in the development of cellular resistance to chemical stresses of various kinds (either by transport of the offending chemical out of the cell or by modification of the chemical to a less hazardous substance) should increase the fitness of the organism in the environment containing the hazardous substance (i.e., large-scale fermentative culture), and thereby may permit relatively larger numbers of cells to survive in such a culture. The net effect of all of these mutagenesis strategies is to increase the quantity of fine-chemical-producing compounds in the culture, thereby increasing the yield, production, and/or efficiency of production of one or more desired fine chemicals from the culture.

This aforementioned list of mutagenesis strategies for SRT proteins to result in increased yields of a desired compound is not meant to be limiting; variations on these mutagenesis strategies will be readily apparent to one of ordinary skill in the art. By these mechanisms, the nucleic acid and protein molecules of the invention may be utilized to generate *C. glutamicum* or related strains of bacteria expressing mutated SRT nucleic acid and protein molecules such that the yield, production, and/or efficiency of production of a desired compound is improved. This desired compound may be any natural product of *C. glutamicum*, which includes the final products of biosynthesis pathways and intermediates of naturally-occurring metabolic pathways, as well as molecules which do not naturally occur in the metabolism of *C. glutamicum*, but which are produced by a *C. glutamicum* strain of the invention.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patent applications, patents, published patent applications, Tables, and the sequence listing cited throughout this application are hereby incorporated by reference.

TABLE 1: Genes Included in the Application

Function	Lincomycine RESISTANCE PROTEIN 10 KD CHAPERONIN 60 KD CHAPERONIN 60 KD CHAPERONIN 60 KD CHAPERONIN GENERAL STRESS PROTEIN CTC CATALASE (EC 1.11.16) CARBON STARVATION PROTEIN A SUPEROXIDE DISMUTASE [MN] (EC 1.15.1.1) SUPEROXIDE DISMUTASE [MN] PHOSPHINOTHRICIN-RESISTANCE PROTEIN PHOSPHINOTHRICIN-RESISTANCE PROTEIN
NT Stop	30483 348 16002 1601 203 5865 594 87008 87476 15252
NT Start	29041 52 14389 363 802 7412 2909 86877 87351 14716
Contig	GR00424 GR00124 VV0086 GR00124 GR00353 GR00159 GR00089 VV0098 VV0098 VV0098
Identification Code	RXA01524 RXA00493 RXN00493 F RXA00498 RXA01217 RXA00404 RXN03119 RXN03120 RXN00575 F RXA00575
Amino Acid SEQ ID NO	249 801149 20149 20149
Nucleic Acid SEQ ID NO	1 10 11 11 11 11 12 13

Chaperones

Function Moleculares chaperon (HSP70/DnaK family) Molecular chaperones (HSP70/DnaK family) DNAJ PROTEIN GRPE PROTEIN DNAK PROTEIN DNAK PROTEIN TRAP1 Molecular chaperone, HSP90 family DNAJ PROTEIN TRIGGER FACTOR PS1 PROTEIN VORLÄUFER	PSI PROTEIN VORLAUFER PSI PROTEIN VORLAUFER PSI PROTEIN VORLAUFER PREPROTEIN TRANSLOKASE SECE UNTEREINHEIT PREPROTEIN TRANSLOKASE SECE UNTEREINHEIT PROTEIN-EXPORT MEMBRANE PROTEIN SECD Signal Erkennung particle GTPase /O/C Thioredoxin-ähnliche oxidoreductase THIOL PEROXIDASE (EC 1.11.1.)
NT Stop 3432 6 12473 13865 20178 14522 26 1480 13541 1582 631	1069 3486 31575 13749 5954 6058 24 8533
NT Start 4883 1172 13657 14518 22031 16375 1849 1145 12396 2928 42941	2832 1906 31243 11932 7795 5363 1172 8039
Contig VV0123 GR00391 GR00726 GR00726 VV0057 GR00726 VV0152 GR00242 VV0251 VV0017 VV0018	W0022 W0026 W0026 W0124 W0171 W0119 W0206
Identification Code RXN01345 F RXA01345 F RXA01345 RXA02541 RXA02543 F RXA02543 F RXA02280 F RXA02886 RXN03038 RXN03039 RXN03039 RXN03040	RXN03051 RXN03054 RXN02462 RXN02462 RXN01559 RXN01863
Amino Acid SEQ ID NO 24 10 NO 30 30 30 30 44 44 46 46 46 46 46 46 46 46 46 46 46	8 8 8 8 8 8
Nucleic Acid SEQ ID NO 23 12 25 29 33 33 35 41 45 47	

	Function	THIOL:DISULFIDE AUSTAUSCH PROTEIN DSBD	THIOREDOXIN	THIOREDOXIN	PEPTIDYL-PROLYL CIS-TRANS ISOMERASE (EC 5.2.1.8)	PEPTID KETTE RELEASE FACTOR 3	PEPTID KETTE RELEASE FACTOR 3 PUTATIVES OVERSOON FORDERS	SMALL COLD-SHOCK PROTEIN OPCA	SMALL COLD-SHOCK PROTEIN
	NT Stop	11304	42706	6393	7879	14.	518 14556		3665
Table 1 (continued)	NT Start	12059 836	42335	5527	7103	- :	13600		3465
ab e	Contig.	W0179 W0223	W0079	W0047	W0320	VV0284	W0074		GR00549
	Identification Code	RXN01676 RXN00380	RXN00937	RXN02325	RXN01837	RXN02002	RXN02736	RXS03217	TRANSITY I
	Amino Acid SEQ ID NO	99 99	2 8	2 2	. %	9 2	8	82	
	Nucleic Acid SEQ ID NO	65 67					29		

Proteins involved in stress responses

Function	COLD SHOCK-LIKE PROTEIN CSPC SMALL COLD-SHOCK PROTEIN PROBABLE HYDROGEN PEROXIDE-INDUCIBLE GENES ACTIVATOR damage-inducible protein P OSMOTICALLY INDUCIBLE PROTEIN C probable metallothionein u0308aa - Mycobadenium leprae	LYTB PROTEIN LYTB PROTEIN LYTB PROTEIN DIADENOSINE 5',5"-P1,P4-TETRAPHOSPHATE HYDROLASE (EC 3.6.1.17) DIADENOSINE 5',5"-P1,P4-TETRAPHOSPHATE HYDROLASE (EC 3.6.1.17) EXOPOLYPHOSPHATASE (EC 3.6.1.11)	GUANOSINE-3',5'-BIS(DIPHOSPHATE) 3'-PYROPHOSPHOHYDROLASE (EC 3.1.7.2) EXOPOLYPHOSPHATASE (EC 3.6.1.11) EXOPOLYPHOSPHATASE (EC 3.6.1.11)
NT Stop	19248 992 2771 1192 11206 1633	706 6768 16749 2774	10045 16535 2353
NT Start	19628 792 1878 2 2 11640 551	1680 5761 17276 3259	15609 15609 2763
Contig.	GR00641 GR00218 GR00467 GR00708 GR10006 GR10006	W0321 W0143 W0050 W0319	VV0007 VV0319
Identification Code	RXA02184 RXA00810 RXA01674 RXA02431 RXA0246 RXA02861	RXN00786 RXS01027 RXS01528 RXS01716 RXS01835	RXS02497 RXS02972
Amino Acid SEQ ID NO	88 89 92 88 88 88 88 88 88 88 88 88 88 88 88 88	5	110 112
Nucleic Acid SEQ ID NO	8	3 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	109 111

Resistance and tolerance

Function	ARGININE HYDROXIMATE RESISTANCE PROTEIN ARSENATE REDUCTASE ARSENICAL-RESISTANCE PROTEIN ACR3 BACITRACIN RESISTANCE PROTEIN (PUTATIVE UNDECAPRENOL KINASE) (EC 2.7.1.66)
NT Stop	6743 6199 1457 1843 5760 6916 8993 3201
NT Start	6231 5837 1843 2940 4651 6278 9871
Contig.	GR00640 GR00159 GR00159 GR00646 GR00646 GR00646 GR00646
	RXA02159 RXA02201 RXA00599 RXA02200 RXA02202 RXA02205 RXA00900
Amino Acid SEQ ID NO	114 116 118 120 122 124 126 128
Nucleic Acid SEQ ID NO	55 52 52 53 53 54 55 55 57 57 57 57 57 57 57 57 57 57 57

							80		ROTEIN DRBA	5			NE PROTEIN																						SOR	SOR										
Function		BICYCLOMYCIN RESISTANCE PROTEIN	BICYCLOMYCIN RESISTANCE PROTFIN	CHLORAMPHENICOL RESISTANCE PROTEIN	CHLORAMPHENICOL RESISTANCE PROTEIN	CHLORAMPHENICOL RESISTANCE PROTEIN	COPPER RESISTANCE PROTEIN C PRECURSOR	COPPER RESISTANCE PROTEIN C PRECURSOR	DAUNORUBICIN RESISTANCE ATP-BINDING PROTEIN DREA	DAUNORUBICIN RESISTANCE PROTEIN	AUNORUBICIN RESISTANCE PROTEIN	AUNORUBICIN RESISTANCE PROTEIN	DAUNORUBICIN RESISTANCE TRANSMEMBRANE PROTEIN	METHYLENOMYCIN A RESISTANCE PROTEIN	METHYLENOMYCIN A RESISTANCE PROTEIN	MET INTLENOMYCIN A RESISTANCE PROTEIN	METHY COUNCIL A RESISTANCE PROTEIN	METHY ENOMINE A RESISTANCE PROTEIN	MYCINAMICIN DESIGNATOR SOCIETY	MACROLIDE EFFELLY DECTENT	CATALOGICATION TROLEIN	MICKEL DESIGNATION STORY	INDI ONE DESIGNATION NOON PROFESSION	CHINOLONE RESISTANCE NORA PROTEIN	INOLONE RESISTANCE NORA PROTEIN	QUINOLONE RESISTANCE NORA PROTEIN	QUINOLONE RESISTANCE NORA PROTEIN	QUINOLONE RESISTANCE NORA PROTEIN	TELLURIUM RESISTANCE PROTEIN TERC	DAUNOMYCIN C-14 HYDROXYLASE	VIDRICIDACI IN UTILIZATION PROTEIN VIUB	MERGURIC REDUCTASE (EC. 1.16.1.1)	MERCURIC REDUCTASE (EC 1.16.1.1)	MERCURIC REDUCTASE (EC 1.16.1.1)	HEAVY METAL TOLERANCE PROTEIN PRECURSOR	HEAVY METAL TOLERANCE PROTEIN PRECURSOR	VANZ PROTEIN, teicoplanin resistance protein	Hypothetical Drug Resistance Protein	Appendical Drug Resistance Protein	MUCHINANG RESISTANCE PROTEIN B	Hypothetical Drug Resistance Protein	Hypothetical Drug Transporter	hypothetical Drug Transporter Hypothetical Drug Transporter	othetical Drug Transporter	Appothetical Drug Transporter	
Stop	•	_		_	1811 C					_				.						-								_								_	_			_		_				
tinued		æ	88	4	8	4	265	202	9	9	256	8	283	20.5	3010	4464	3183	1109	339	4	A075	982	4894	4	4612	.2917	6714	တ	2147	1543	3580	3706	4191	4717	1245	ء م	20 g	1048	1839	000	3216	2120	14101	963	765	
Table 1 (continued)		8581	435/	3263	. 1515	282	9/1	176	1/63	7950	,		1023	3232d 4660	20.00	4384	2031	ر ا	-	40116	9626	10246	3776	774	5754	3807	7931	911	2000	2367	3236	3398	3772	4229	800	- 50	2054	855	16933	8058	2491	1395	16290	4	4	
Table Contig		0000	GR00245	GR00046	VV0056	GR005/4	GR00015	GROOTS	GR00283	OBLOVA CEOURI	GR00224	GK00223	GR00283	GR00214	GR00410	GR00410	W0020	GR00552	GR00626	W0127	GR00555	GR00555	W0209	GR00288	W0136	GR00323	VV0102	GROUGS	GROOKS	GR00013	GR00228	GR00296	GR00296	GK00296	SPOODS GBOOSES	GR00282	W0248	GR00535	W0020	GR00655	VV0042	GR10044	GR00119	VV0108	GR00336	
Identification Code	TOO ON A	E DYACCOL	DVACCOON	DVN(04004	E DYACLOS	RXA00100	RX A DO 1 DO	PXA0006	RXNOROS	F RX AOOR 20	F PXA00834	RXADOOS	RXNOORDS	F RXA00803	RXA01407	RXA01408	RXN01922	F RXA01922	RXA02060	RXN01936	F RXA01936	F RXA01937	RXN01010	F RXA01010	RXN03142	F KXA01150	F RYAN2146	RXADORFR	RXA02305	RXA00084	RXA00843	RXA01052	FXA01053	RXN03123	F RXA00993	RXA01051	RXN01873	F RXA01873	RXN00034	F RXA02273	RXN03075	F RXA02907	RXA00479	RXN03124	F RXA01180	
Amino Acid	130	133	125	35	3 5	140	142	14	146	148	150	152	2 2	156	158	160	162	<u>\$</u>	166	168	170	172	174	176	1/8				188		192		96	300	202	30				_	214	_		220		
Nucleic Acid	129	131	133	135	137	139	141	143	145	147	149	151	153	155	157	159	16 1	163	5 <u>5</u>	/ 0	1 69	<u> </u>	575	5 <u>£</u>				185				195					205				213			2 817		

	Function	Hynothetical Data Transfer	Hypothetical Data Tenantical	Hypothetical Drio Tababotes		Multiperior February Devices of the Multiperior of	MINITIDE ID DECISTATION DOCUMENT		MINITION OF STREET STRE		MULTIDADG RESISTANCE PROTEIN B		MULIDRUG RESISTANCE PROTEIN B	MULIDRUG RESISTANCE PROTEIN B	MULTIDRUG RESISTANCE PROTEIN B	MULTIDRUG RESISTANCE PROTEIN B		MULTIDRUG RESISTANCE PROTEIN B	MULIIDRUG RESISTANCE PROTEIN B	BMRO PROTEIN Bacillus subtilis bmro, multidrug efflux transporter	Hypothetical Drug Transporter	Hypothetical Drug Permease	Hypothetical Drug Resistance Protein	Hypothetical Drug Transporter	Typotnetical Urug Transporter	MUCHURUG RESISTANCE PROTEIN B	M TOINAMICIN-RESISTANCE PROTEIN MYRA	MILETIDE OF STREET STRE	MILITION OF RESISTANCE-LIKE ATP-BINDING PROTEIN MDL	MUCHIDROG RESISTANCE-LIKE ATP-BINDING PROTEIN MOL	CHI COMMENCE NOTE NORA PROTEIN	A201A DECISTANCE RESISTANCE PROTEIN	DALINION INC. A IP-BINDING PROTEIN	MAZO BEOTEIN	MEDCIPIA TO ALONDE TO THE TOTAL	MEDITION TRANSPORT PROTEIN PERIPLASMIC COMPONENT PRECURSOR	CADMIUM EFFILIX SYSTEM ACCESSORY PROTEIN COMPONENT PRECURSOR	SOURCE TROISING TO THE TROISING THE TROISING TO THE TROISING			
(Pail	NT Stop	10027	10253	1835	1236	203	3683	11855	15294	6223	5864	1484	2 5	2 4	200	200	000	9000	4 5	S E	973	250	4440	7617	20320	26.7	1360	- 3335 511	-	ru	1860	10338	4884	3648	9	5610	3 4	2383	294	4424	
Table 1 (continued)	NT Start	10296	12343	2440	1841	1684	2307	13252	13834	4892	4802	1837	2743	13146	744	1070	11407	1107	1423	7070	8204 8204	3264	972	25201	5155	1173	13120	85.50	489	547	3275	8992	6128	3424	11242	7124	267	2150	527	4056	
Table	Contig.	GR00741	GR00741	W0018	GR10035	GR00450	GR00463	GR00009	GR00032	W0038	GR00151	GR10016	GR00160	W0082	GROO382	GROO383	WO082	GROOSE	GR00439	GEOOGS	GR00629	GROOM	V0108	W0135	W0219	W0076	W0171	W0002	W0163	W0358	W0232	W0169	W0059	VV0321	VV0102	W0137	VV0326	W0149	W0234	VV0057	
	Identification Code	RXA02586	RXA02587	FXN03042	F KXA02893	RXA01616	KXA01666	RXA00062	RXA00215	RXN03064	F RXA00565	F RXA02878	RXA00648	RXN01320	F RXA01314	F RXA01320	PXN02926	F RXA01319	RXA01578	RXA02087	RXA02088	RXA00764	RXN03125	RXN01553	RXN00535	RXN00453	RXN00932	RXN03022	RXN03151	RXN02832	RXN00165	RXN01190	RXN01102	RXN00788	RXN02119	PXN01605	RXN01091	RXS02979	RXS02987	RXS03095	
	Amino Acid SEQ ID NO	224	97,	930	000	232	\$ 6	236	238	240	242	244	246	248	250	252	254	256	258	260	262	264	3 66	268	270	272	274	276	278	280	282	284	286	288	290	292	294	96.	298	300	
	Nucleic Acid SEQ ID NO	223	7.66	220	324	22.	350	227	336	£23	241	243	245	247	249	521	253	255	257	259	261	263	265	267	569			_		_			782				293			_	

Gen Bank** Gene Name Gene Function Reference A09073 Ppg Phosphoenol pyruvate carboxylase Bachnam, Be tal. "DNA fragment coding for phosphoenol-pyruvate carboxylase, recombinant DNA carrying of recombinant DNA carrying carrying of recombinant DNA carrying carryi			TABLE 2 - Excluded Genes	ded Genes
PPG Phosphoenol pyruvate carboxylase Threonine dehydratase murC; ftsQ; ftsZ dtsR1; dtsR2 dtsR1; dtsR2 dtsR1; dtsR2 gttB; gttD gttB; gttD gttB; gttD gttB; gttD gttB; gttD dehydratase rep rep rep; aad glnA Glutamine synthetase argC dehydrogenase argC dehydrogenase glnA Glutamine synthetase argC dehydrogenase argC dehydrogenase argC dehydrogenase argC dehydrogenase argC Agminiosuccinate synthetase argC Omithine carbamolytransferase argF Omithine carbamolytransferase argF Dyruvate carboxylase	GenBank TM Accession No.	Gene Name	uo	Reference
murC; ftsQ; ftsZ murC; ftsQ; ftsZ dtsR1; dtsR2 tkt murI dtsR1; dtsR2 gttB; gttD gltB; gttD acn acn acn acn acn acn acn ac	A09073	ррв		Bachmann, B. et al. "DNA fragment coding for phosphoenolpyruvat corboxylase, recombinant DNA carrying said fragment, strains carrying the recombinant DNA and method for producing L-aminino acids using said strains." Patent: FP 0358940.4 3 0320 too.
murC; ftsQ; ftsZ dtsR dtsR1; dtsR2 murI murI tkt murI murI dtsR1; dtsR2 gltB; gltD gltB; gltD gltB; gltD aconitase rep Replication protein rep; aad aconitase rep; aad glnA Glutamine synthetase dehydrogenase glnA Glutamine synthetase argC Argininosuccinate synthetase argC Argininosuccinate dehydratase argC Argininosuccinate dehydratase argC Argininosuccinate dehydratase pyc Pyruvate carboxylase	A45579, A45581, A45583, A45585		Threonine dehydratase	Moeckel, B. et al. "Production of L-isoleucine by means of recombinant micro-organisms with deregulated threonine dehydratase," Patent: WO 9519442-A 5 07/20/95
dtsR i, dtsR2 dtsR i, dtsR2 murl murl murl tkt murl D-glutamate racemase tkt transketolase gltB; gltD gltB; gltD acn acn acn acn Replication protein rep; aad argC N-acetylglutamate-5-semialdehyde dehydrogenase argG Argininosuccinate synthetase argG Argininosuccinate synthetase argB Ormithine carbamolytransferase argB Argininosuccinate synthetase argB Pyruvate carboxylase	AB003132	murC; ftsQ; ftsZ		Kobayashi, M. et al. "Cloning, sequencing, and characterization of the ftsZ gene from coryneform bacteria," Biochem. Biophys. Res. Commun.
dtsR1; dtsR2 tkt murl Deglutamate racemase tkt transketolase Glutamine 2-oxoglutarate aminotransferase large and small subunits acn acn aconitase rep; aad Replication protein; aminoglycoside adenyltransferase argC N-acetylglutamate-5-semialdehyde dehydrogenase glnA Glutamine synthetase argG Argininosuccinate synthetase argG Argininosuccinate synthetase argC Omithine carbamolytransferase aroD 3-dehydroquinate dehydratase pyc Pyruvate carboxylase	AB015023	murC; ftsQ		Wachi, M. et al. "A murC gene from Coryneform bacteria," Appl. Microbiol. Riotechnol 51(2):223 229 (1900)
I murl D-glutamate racemase tkt transketolase gltB; gltD Glutamine 2-oxoglutarate aminotransferase large and small subunits acn aconitase rep Replication protein rep; aad Replication protein; aminoglycoside argC N-acetylglutamate-5-semialdehyde dehydrogenase dehydrogenase argG Argininosuccinate synthetase argF Omithine carbamolytransferase aroD 3-dehydroquinate dehydratase pyc Pyruvate carboxylase	AB018530	dtsR		Kimura, E. et al. "Molecular cloning of a novel gene, dtsR, which rescues the detergent sensitivity of a mutant derived from <i>Brevibacterium</i>
t tkt gltB; gltD acn rep; aad rep; aad argC argC argG argF aroD pyc	AB018531	dtsR1; dtsR2		idctofermentum, Biosci. Biotechnol. Biochem., 60(10):1565-1570 (1996)
gltB; gltD acn rep; aad argC glnA hisF argG argF aroD pyc	AB020624	murl	D-glutamate racemase	
gltB; gltD rep; aad argC glnA hisF argG argF aroD pyc	AB023377	tkt		
acn rep ad rep; aad argC argF aroD pyc	AB024708	gltB; gltD	Glutamine 2-oxoglutarate aminotransferase large and small subunits	
rep; aad argC glnA hisF argG argF aroD pyc	AB025424	acn		
argC glnA hisF argG argF aroD pyc	AB027714	rep	Replication protein	
argC glnA hisF argG argF aroD pyc	AB027/15	rep; aad	Replication protein; aminoglycoside adenyltransferase	
glnA hisF argG argF aroD pyc	AF005242	argC	N-acety/glutamate-5-semialdehyde dehydrogenase	
hisF argG argF aroD pyc	AF005635	glnA	Glutamine synthetase	
argG aroD pyc	AF030405	hisF	cyclase	
argF aroD pyc	AF030520	argG	Argininosuccinate synthetase	
aroD pyc	AF031518	argF	Ornithine carbamolytransferase	
pyc	AF036932	aroD	3-dehydroquinate dehydratase	
	AF038548	pyc	Pyruvate carboxylase	



Ar03865	dei A F. ant. ral	manumos) = are:	(Daniel
		Dipopulae-binding protein; adenine phosphoribosyltransferase; GTP	Wehmeier, L. et al. "The role of the Corynebacterium glutamicum rel gene in (p)ppGpp metabolism," <i>Microbiology</i> 144-1853, 1863, 1969.
AF041436	argR	Arginine repressor	(052) 7001-5501111
AF045998	Admi	- British Colored	
A F048764	Поло	monophosphate phosphatase	
AF049897	angri	Argininosuccinate lyase	
	ange, angu, angu,	N-acetylglutamylphosphate reductase:	
	argu; argr; argk;	ornithine acetyltransferase; N-	
	argo; argn	acetylglutamate kinase; acetylomithine	
		transminase; ornithine	
		carbamoyltransferase: arginine repressor:	
		argininosuccinate synthase:	
10000		argininosuccinate Ivase	
Ar050109	inhA	Enovi-acyl carrier protein raduction	
AF050166	hisG	ATP phoene it	
AF051846	hisA	The principlion of the principli	
		Phosphoribosylformimino-5-amino-1-	
		pnosphoribosyl-4-imidazolecarboxamide	
AEnsaksa		isomerase	
70700	шега	Homoserine O-acetyltransferase	Park C et al "Inclusion"
			and the control of th
A E062071			Call. 9/21/20/20/20/20/20/20/20/20/20/20/20/20/20/
r0330/1	aroB	Dehydroguinate synthetase	(3)7.780-294 (1998)
AF060558	hisH	Glutamine amidotron 6	
AF086704	hisE	December 1 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	
٠		rnosphoribosyl-ATP.	
AF114233	Acre	pyrophosphohydrolase	
	COR	3-enolpyruvylshikimate 3-phosphate	
AF11619A		synthase	
		L-aspartate-alpha-decarboxylase precursor	Disch V et al
			Custil, 14. et al. Expression of the Corynebacterium glutamicum panD gene
			circuling L-aspartate-alpha-decarboxylase leads to pantothenate
A E124610			Overproduction in Escherichia coli," Appl. Environ. Microbiol., 65(4)1530.
F124518	aroD; aroE	3-dehydroquinase: shikimate	(6661) 6501
A E 124600		dehydrogenase	
124000	aroC; aroK; aroB;	Chorismate synthase: shikimate kinase: 3	
	DepC	dehydroquinate synthase; putative	
A E145007		cytoplasmic peptidase	
140641 14	InhA		

A 1001436	9,00	Table 2 (continued	inued)
00010000	ect	Transport of ectoine, glycine betaine, proline	Peter, H. et al. "Corynebacterium glutamicum is equipped with four secondary carriers for compatible solutes: Identification, sequencing, and characterization of the proline/ectoine uptake system, ProP, and the ectoine/proline/glycine
AJ004934	dapD	Tetrahydrodipicolinate succinylase (incomplete)	Wehrmann, A. et al. "Different modes of diaminopimelate synthesis and their role in cell wall integrity: A study with Corynebacterium glutamicum," J. Borteriol 180(12):2150-2156-2156-2156
AJ00/132	ppc; secG; amt; ocd; soxA	Phosphoenolpyruvate-carboxylase; ?; high affinity ammonium uptake protein; putative omithine-cyclodecarboxylase; sarcosine oxidase	(966) (1010-2010-1010)
AJ010319	fts Y, gln B, gln D, srp; amt P	Involved in cell division; PII protein; uridylyltransferase (uridylyl-removing enzmye); signal recognition particle; low affinity ammonium untake protein	Jakoby, M. et al. "Nitrogen regulation in Corynebacterium glutamicum; Isolation of genes involved in biochemical characterization of corresponding proteins," FEMS Microbiol., 173(2):303-310 (1999)
AJ132968 AJ224946	cat	Chloramphenicol aceteyl transferase	
		L-malate: quinone oxidoreductase	Molenaar, D. et al. "Biochemical and genetic characterization of the membrane-associated malate dehydrogenase (acceptor) from Corynebacterium
AJ238250	ndh	NADH dehydrogenase	5
7430	porA	Porin	Lichtinger, T. et al. "Biochemical and biophysical characterization of the cell wall porin of Corynebacterium glutamicum: The channel is formed by a low molecular mass polynegister." Biochemical
6747		Transposable element IS31831	Vertes et al. "Isolation and characterization of IS31831, a transposable element
D84102	OdhA	2-oxoglutarate dehydrogenase	Usuda, Y. et al. "Molecular cloning of the Corynebacterium glutamicum (Brevibacterium lactofermentum AJ12036) odhA gene encoding a novel type
E01338	hdh; hk	Homoserine dehydrogenase; homoserine kinase	Katsumata, R. et al. "Production of L-thereonine and L-isoleucine," Patent: JP 1987232302-A 1 10/12/82
501339		Upstream of the start codon of homoserine kinase gene	Katsumata, R. et al. "Production of L-thereonine and L-isoleucine," Patent: JP
E01375		Tryptophan operon	10/71/01 7 17/77/77
13/0	прь; пре	Leader peptide; anthranilate synthase	Matsui, K. et al. "Tryptophan operon, peptide and protein coded thereby, utilization of tryptophan operon gene expression and production of tryptophan," Patent: JP 1987244382-A 1 10/24/87
			0.140
	T		

	Table 2 (continued	inied)
E01377	Promoter and operator regions of tryptophan operon	Matsui, K. et al. "Tryptophan operon, peptide and protein coded thereby, utilization of tryptophan operon gene expression and production of
E03937	Biotin-synthase	Hatakeyama, K. et al. "DNA fragment containing gene capable of coding
E04040	Diamino pelargonic acid aminotransferase	Biotin synthetase and its utilization," Patent: JP 1992278088-A 1 10/02/92 Kohama, K. et al. "Gene coding diaminopelargonic acid aminotransferase and desthiobiotin synthetase and its utilization," Patent: JP 1992330284-A 1
E04041	Desthiobiotinsynthetase	Kohama, K. et al. "Gene coding diaminopelargonic acid aminotransferase and desthiobiotin synthetase and its utilization," Patent: JP 1992330284-A 1
E04376		Kurusu, Y. et al. "Gene DNA coding aspartase and utilization thereof," Patent: JP 1993030977-A 1 02/09/03
E04377		Katsumata, R. et al. "Gene manifestation controlling DNA," Patent: JP 1993056782-A 3 03/09/93
E04484	Isocitric acid lyase N-terminal fragment	Katsumata, R. et al. "Gene manifestation controlling DNA," Patent: JP
FOSTOR	Prephenate dehydratase	Sotouchi, N. et al. "Production of L-phenylalanine by fermentation," Patent: JP
E05113	Aspartokinase	Fugono, N. et al. "Gene DNA coding Aspartokinase and its use," Patent: JP
21172	Dihydro-dipichorinate synthetase	dipicolinic acid synthetase
E05/70	Diaminopimelic acid dehydrogenase	Kobayashi, M. et al. "Gene DNA coding Diaminopimelic acid dehydrogenase
E037/9	Threonine synthase	Kohama, K. et al. "Gene DNA coding threonine synthase and its use," Patent: JP 1993284972-A 1 11/02/02
01100	Prephenate dehydratase,	Kikuchi, T. et al. "Production of L-phenylalanine by fermentation method,"
E06146	Mutated Prephenate dehydratase	Kikuchi, T. et al. "Production of L-phenylalanine by fermentation method," Patent: 1P 1993344881. A 1.327233
E06825	Acetohydroxy acid synthetase	Inui, M. et al. "Gene capable of coding Acetohydroxy acid synthetase and its
E06826	Aspartokinase	Sugimoto, M. et al. "Mutant aspartokinase gene," patent: JP 1994062866-A 1 03/08/94
	Mutated aspartokinase alpha subunit	Sugimoto, M. et al. "Mutant aspartokinase gene," patent: JP 1994062866-A 1 03/08/94

F06827		Table 2 (continued)	inued)	
E02701		Mutated aspartokinase alpha subunit	Sugimoto, M. et al. "Mutant aspartokinase gene," patent: JP 1994062866-A 1 03/08/94	
10//01	secY		Honno, N. et al. "Gene DNA participating in integration of membraneous	
EU&1 / /		Aspartokinase	Sato, Y. et al. "Genetic DNA capable of coding Aspartokinase released from	
E08178,		Feedback inhibition-released Aspartokings	reedback inhibition and its utilization," Patent: JP 1994261766-A 1 09/20/94	
E08179, E08180,		Dealine and a company of the company	Satus, T. et al. "Genetic DNA capable of coding Aspartokinase released from feedback inhibition and its utilization." Patent: JP 1994261765. A 1 0020004	
E08181, E08182			46/07/60 I V-00/1074/7	
E08232		Acetohydroxy-acid isomeroreductase	Inui, M. et al. "Gene DNA coding acetohydroxy acid isomeroreductase."	
E08234	secE		Asai, Y. et al. "Gene DNA coding for translanding and the coding for translanding for trans	
E08643		FT aminotromeforms L 1 - 1 - 1 - 1 - 1	Patent: JP 1994277073-A 1 10/04/94	
		Synthetase promoter region	Hatakeyama, K. et al. "DNA fragment having promoter function in	
E08646		Biotin synthetase	Hatakeyama, K. et al. "DNA fragment having and the control of the	
E08649		**************************************	coryneform bacterium," Patent: JP 1995031476-A 1 02/02/05	
		Aspanase	r function in coryneform	- 6
E08900		Dihydrodipicolinate reductase		i4 -
E08901		Diaminonimalic coid decade	acid reductase and utilization thereof," Patent: JP 1995075578-A 1 03/20/05	
703013		Diaminophiliene acid decarboxylase	Madori, M. et al. "DNA fragment containing gene coding Diaminopimelic acid	
12394		Serine hydroxymethyltransferase	Hatakeyama, K. et al. "Production of L-trypophan," Patent: JP 1997028391-A	
E12760, E12759,		transposase	Moriya, M. et al. "Amplification of gene using artificial transposon," Patent:	
E12764		,	1970/0221-A US/18/9/	
200		Arginyl-tRNA synthetase; diaminopimelic acid decarboxylase	Moriya, M. et al. "Amplification of gene using artificial transposon," Patent:	
(9/7)a		Dihydrodipicolinic acid synthetase	Moriya, M. et al. "Amplification of gene using artificial transposon," Patent:	
E12770		aspartokinase	Moriya, M. et al. "Amplification of gene using artificial transposon," Patent:	
E12773		Dihydrodipicolinic acid reductase	Moriya, M. et al. "Amplification of gene using artificial transposon," Patent:	
			JP 1997070291-A 03/18/97	

E13655		Table 2 (continued)	inued)
101508		Glucose-6-phosphate dehydrogenase	Hatakeyama, K. et al. "Glucose-6-phosphate dehydrogenase and DNA capable of coding the same," Patent: JP 199722461.4 1 00,02,02
900100	IIVA	Threonine dehydratase	Moeckel, B. et al. "Functional and structural analysis of the threonine dehydratase of Corynebacterium glutamicum," J. Bacteriol., 174:8065-8072 (1992).
L07603	EC 4.2.1.15	3-deoxy-D-arabinoheptulosonate-7- phosphate synthase	Chen, C. et al. "The cloning and nucleotide sequence of Corynebacterium glutamicum 3-deoxy-D-arabinoheptulosonate-7-phosphate synthase gene," FEMS Microbiol 1 of 102, 2020, 100, 100, 200, 200, 200, 200
L09232 L18874	IIvB; iivC	Acetohydroxy acid synthase large subunit; Acetohydroxy acid synthase small subunit; Acetohydroxy acid isomeroreductase	Keilhauer, C. et al. "Isoleucine synthesis in Corynebacterium glutamicum: molecular analysis of the ilvB-ilvN-ilvC operon," J. Bacteriol., 175(17):5595-5603 (1993)
		Phosphoenolpyruvate sugar phosphotransferase	Fouet, A et al. "Bacillus subtilis sucrose-specific enzyme II of the phosphotransferase system: expression in Escherichia coli and homology to enzymes II from enteric bacteria," PNAS USA, 84(24):8773-8777 (1987); Lee, J.K. et al. "Nucleotide sequence of the gene encoding the Corynebacterium glutamicum mannose enzyme II and analyses of the deduced protein sequence." FEMS Microbiol 1911, 1
127123	асеВ	Malate synthase	Lee, H-S. et al. "Molecular characterization of aceB, a gene encoding malate synthase in Corynebacterium glutamicum," J. Microbiol. Biotechnol., 4(4):256-263 (1994)
071177		Pyruvate kinase	Jetten, M. S. et al. "Structural and functional analysis of pyruvate kinase from Corynebacterium glutamicum," Appl. Environ. Microbiol., 60(7):2501-2507 (1994)
128/60	aceA	Isocitrate lyase	
233900	dbr.	Diphtheria toxin repressor	Oguiza, J.A. et al. "Molecular cloning, DNA sequence analysis, and characterization of the Corynebacterium diphtheriae dtxR from Brevibacterium lactofermentum". J. Bacteriol. 1777).465, 467, 1908.
113774		Prephenate dehydratase	Follettie, M.T. et al. "Molecular cloning and nucleotide sequence of the
MI6175	5S rRNA		Park, Y-H. et al. "Phylogenetic analysis of the coryneform bacteria by 56 rRNA sequences." J. Bacterial 160-1801 1906 (1905)
M110003	ம்	Anthranilate synthase, 5' end	Sano, K. et al. "Structure and function of the trp operon control regions of Brevibacterium lactofermentum, a glutamic-acid-producing bacterium," Gene, 52:191-200 (1987)
M10004	trpA	Tryptophan synthase, 3'end	Sano, K. et al. "Structure and function of the trp operon control regions of Brevibacterium lactofermentum, a glutamic-acid-producing bacterium," Gene, 52:191-200 (1987)

aecD; brnQ; yhbw Beta C-S lyase; branched-chain amino acid uptake carrier; hypothetical protein yhbw trpD Leader gene (promoter) trpD Anthranilate phosphoribosyltransferase cgllM; cgllR; clgllR methyltransferase; putative type II seyrosoine recA ppx recA proC L-proline: NADP+ 5-oxidoreductase cobg; proB; unkdh isomer specific 2-hydroxyacid dehydrogenases cdehydrogenases	M25819		Table 2 (continued)	inued)
23S rRNA gene insertion sequence 23S rRNA gene insertion sequence Beta C-S lyase; branched-chain amino acid uptake carrier; hypothetical protein yhbw trpD Leader gene (promoter) Anthranilate phosphoribosyltransferase eglIM; cglIR; clglIR Putative type II 5-cytosoine methyltransferase; putative type II restriction endonuclease; putative type II restriction endonuclease ppx // ppt III restriction endonuclease proC L-proline: NADP+ 5-oxidoreductase loobg; proB; unkdh 7; gamma glutamyl kinase; similar to D- isomer specific 2-hydroxyacid dehydrogenases			Phosphoenolpyruvate carboxylase	O'Regan, M. et al. "Cloning and nucleotide sequence of the
1 aecD; brnQ; yhbw Beta C-S lyase; branched-chain amino acid uptake carrier; hypothetical protein yhbw britable. 1 trpD Anthranilate phosphoribosyltransferase methyltransferase; putative type II restriction endonuclease; putative type I restriction endonuclease; putative type I restriction endonuclease. 1 proC L-proline: NADP+ 5-oxidoreductase be some specific 2-hydroxyacid dehydrogenases	M85106		238 rBNA gene incertion gogges	glutamicum ATCC13032," Gene, 77(2):237-251 (1989)
aecD; brnQ; yhbw Beta C-S lyase; branched-chain amino acid uptake carrier; hypothetical protein yhbw Leader gene (promoter) trpD Anthranilate phosphoribosyltransferase cgllM; cgllR; clglR Putative type II 5-cytosoine methyltransferase; putative type II restriction endonuclease putative type I or type III restriction endonuclease process, putative type I or type III restriction endonuclease process, putative type I or type III restriction endonuclease process, putative type I or type III restriction endonuclease process, putative type I or type III restriction endonuclease process, putative type I or type III restriction endonuclease process, putative type I or type III restriction endonuclease process, putative type I or type III restriction endonuclease process process putative type I or type III restriction endonuclease process putative type I or type III restriction endonuclease process putative type I or type III restriction endonuclease process putative type I or type III restriction endonuclease process putative type I or type II restriction endonuclease process putative type I or type II restriction endonuclease process putative type I or type II restriction endonuclease process putative type I or type II restriction endonuclease putative type III restriction endonuclease putative type II restriction en				Roller, C. et al. "Gram-positive bacteria with a high DNA G+C content are characterized by a common insertion within their 23S rRNA genes." J. Gen.
aecD; brnQ; yhbw Beta C-S lyase; branched-chain amino acid uptake carrier; hypothetical protein yhbw trpD Anthranilate phosphoribosyltransferase methyltransferase; putative type II restriction endonuclease; putative type II restriction endonuclease; putative type II restriction endonuclease ppx recA recA ppx recA ppx recA ppx recA ppx recA ppx recA ppx recA recA ppx recA recA ppx recA recA recA ppx recA	M85107,		23S rRNA gene insertion sequence	Microbiol., 138:1167-1175 (1992)
trpD trpD Anthranilate phosphoribosyltransferase eglIM; cgIIR; clgIIR proc recA proc L-proline: NADP+ 5-oxidoreductase obg; proB; unkdh proc L-proline: NADP+ 5-oxidoreductase dehydrogenases dehydrogenases dehydrogenases logical log	MI63108		•	characterized by a common insertion within their 23S rRNA genes." J Gen
trpD cglIM; cglIR; clglIR recA proC Leader gene (promoter) Anthranilate phosphoribosyltransferase methyltransferase; putative type II restriction endonuclease; putative type I or type III restriction endonuclease ppx hpx cA proC L-proline: NADP+ 5-oxidoreductase be dehydrogenases cdhydrogenases	M89931	aecD; brnQ; yhbw	Beta C-S lyase; branched-chain amino acid	Microbiol., 138:1167-1175 (1992)
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trpD Anthranilate phosphoribosyltransferase cgllM; cgllR; clgllR Putative type II 5-cytosoine methyltransferase; putative type II restriction endonuclease ppx ppx recA ppx				Corynebacterium glutamicum ATCC 13032 is directed by the brnQ gene
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trpD Anthranilate phosphoribosyltransferase cglIM; cglIR; clglIR Putative type 11 5-cytosoine methyltransferase; putative type 11 restriction endonuclease; putative type 1 or type III restriction endonuclease recA ppx ppx L-proline: NADP+ 5-oxidoreductase becomes proB; unkdh ?;gamma glutamyl kinase;similar to D. isomer specific 2-hydroxyacid dehydrogenases				hyperproducing strain of Corynebacterium olutamicum: identification
cgllM; cgllR; clgllR Putative type II 5-cytosoine methyltransferase; putative type II restriction endonuclease; putative type I or type III restriction endonuclease ppx ppx trecA ppx trecA proC L-proline: NADP+ 5-oxidoreductase dehydrogenases label dehydrogenases label dehydrogenases				mutation in the trp leader sequence," Appl. Environ. Microbiol. 59(3)-791-700
cgllM; cgllR; clglIR Putative type II 5-cytosoine methyltransferase; putative type II restriction endonuclease type III restriction endonuclease ppx ppx recA ppx type III restriction endonuclease type III restric	U11545	Class	Anthranilate phosphoribosyltmanefamore	(1993)
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methyltransferase; putative type II restriction endonuclease putative type II restriction endonuclease putative type I restriction endonuclease putative type I restriction endonuclease proc ppx ppx recA ppx /-proline: NADP+ 5-oxidoreductase obg; proB; unkdh /-gamma glutamyl kinase; similar to D- isomer specific 2-hydroxyacid dehydrogenases	U13922	collM. collD. clalib		Department, University College Galway, Ireland
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recA ppx roc L-proline: NADP+ 5-oxidoreductase obg; proB; unkdh isomer specific 2-hydroxyacid dehydrogenases			type III restriction endonuclease	13032 and analysis of its role in intergeneric conjugation with Escherichia
ppx proC L-proline: NADP+ 5-oxidoreductase obg; proB; unkdh isomer specific 2-hydroxyacid dehydrogenases				Contraction, 176(23):7309-7319 (1994); Schafer, A. et al. "The
ppx proC L-proline: NADP+ 5-oxidoreductase obg; proB; unkdh isomer specific 2-hydroxyacid dehydrogenases	114066			deficient Escherichia coli etrain." Cara 2000 et 2000
ppx proC L-proline: NADP+ 5-oxidoreductase obg; proB; unkdh ?;gamma glutamyl kinase;similar to D- isomer specific 2-hydroxyacid dehydrogenases	121224	recA		30 and 30
proC L-proline: NADP+ 5-oxidoreductase obg; proB; unkdh ?;gamma glutamyl kinase;similar to D- isomer specific 2-hydroxyacid dehydrogenases	477160	xdd		Ankri, S. et al. "Mutations in the Corvnehacterium chitamiannia
obg; proB; unkdh ?;gamma glutamyl kinase;similar to D-isomer specific 2-hydroxyacid dehydrogenases				biosynthetic pathway: A natural bypass of the proA step." J. Bacteriol
obg; proB; unkdh ?;gamma glutamyl kinase;similar to D-isomer specific 2-hydroxyacid dehydrogenases	J31225	proC	L-proline: NADP+ 5-oxidoreductase	178(15):4412-4419 (1996)
obg; proB; unkdh ?;gamma glutamyl kinase;similar to D-isomer specific 2-hydroxyacid dehydrogenases				Ankri, S. et al. "Mutations in the Corynebacterium glutamicumproline biosynthetic pathway: A natural bypass of the prod. step." I Baccaille
isomer specific 2-hydroxyacid dehydrogenases	J31230	obg; proB; unkdh	Poamma olitamy Vincerii	178(15):4412-4419 (1996)
	·		isomer specific 2-hydroxyacid dehydrogenases	Ankri, S. et al. "Mutations in the Corynebacterium glutamicumproline biosynthetic pathway: A natural bypass of the proA step," J. Bacteriol.
			,	1/8(15):4412-4419 (1996)

thtR; accBC Thiosulfate sulfurtransferase; acyl CoA carboxylase Cmr Multidrug resistance protein aphA-3 3'5"-aminoglycoside phosphotransferase Coynebacterium glutamicum unidentified sequence involved in histidine biosynthesis, partial sequence involved in histidine biosynthesis, partial sequence Tryptophan operon Tr	1131281	F. P.	Table 2 (continued	tinued)
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CipB Heat shock ATP-binding protein aphA-3 37-3"-aminoglycoside phosphotransferase Corynebacterium glutamicum unidentified sequence involved in histidine biosynthesis, partial sequence trpE; trpG; trpD; Tryptophan operon Tryptophan operon Lys A DAP decarboxylase (meso-diaminopimelate decarboxylase, EC 4.1.1.31 EC 4.1.1.31 Phosphoenolpyruvate carboxylase fda Fructose-bisphosphate aldolase 4.2.1.52) AttB-related site Arginyl-tRNA synthetase; Diaminopimelate decarboxylase	U35023	thtR; accBC	Thiosulfate sulfurtransferase; acyl CoA carboxylase	Corynebacterium glutamicum, "Gene, 175:15-22 (1996) Jager, W. et al. "A Corynebacterium glutamicum gene encoding a two-domain protein similar to biotin carboxylases and biotin-carboxyl-carrier protein."
clpB Heat shock ATP-binding protein aphA-3 3'5"-aminoglycoside phosphotransferase Corynebacterium glutamicum unidentified sequence involved in histidine biosynthesis, partial sequence involved in histidine biosynthesis, partial sequence trpA; trpB; trpC; trpD; Iys A DAP decarboxylase (meso-diaminopimelate decarboxylase, EC 4.1.1.20) EC 4.1.1.31 Phosphoenolpyruvate carboxylase fda Fructose-bisphosphate aldolase AttB-related site argS; lysA Arginyl-tRNA synthetase; Diaminopimelate decarboxylase	U43535	cmr	Multidrug resistance protein	Jager, W. et al. "A Corynebacterium glutamicum gene conferring multidrug resistance in the heterologous host Escherichia coli." I Raciazio.
aph.A-3 37-37-aminoglycoside phosphorransferase Corynebacterium glutamicum unidentified sequence involved in histidine biosynthesis, partial sequence trpA; trpB; trpC; trpD; Tryptophan operon Iys A BAP decarboxylase (meso-diaminopimelate decarboxylase (meso-diaminopimelate decarboxylase, EC 4.1.1.20) EC 4.1.1.31 Phosphoenolpyruvate carboxylase fda Fructose-bisphosphate aldolase 1 AttB-related site decarboxylase AttB-related site decarboxylase	U43536	clpB	Heat shock ATP-binding protein	179(7):2449-2451 (1997)
Corynebacterium glutamicum unidentified sequence involved in histidine biosynthesis, partial sequence involved in histidine biosynthesis, partial sequence trpE; trpG; trpL lys A DAP decarboxylase (meso-diaminopimelate decarboxylase, EC 4.1.1.20) EC 4.1.1.31 Phosphoenolpyruvate carboxylase fda Fructose-bisphosphate aldolase 1 L-2, 3-dihydrodipicolinate synthetase (EC 4.2.1.5.2) AttB-related site decarboxylase Arginyl-tRNA synthetase; Diaminopimelate decarboxylase	US3587	aphA-3	3'5"-aminoglycoside phosphotransferase	
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EC 4.1.1.31 Phosphoenolpyruvate carboxylase fda Fructose-bisphosphate aldolase dapA L-2, 3-dihydrodipicolinate synthetase (EC 4.2.1.52) AttB-related site argS; lysA Arginyl-tRNA synthetase; Diaminopimelate decarboxylase	X07563	lys A	DAP decarboxylase (meso-diaminopimelate decarboxylase, EC 4.1.1.20)	Yeh, P. et al. "Nucleic sequence of the lysA gene of Corynebacterium glutamicum and possible mechanisms for modulation of its expression." Mal
fda Fructose-bisphosphate aldolase dapA L-2, 3-dihydrodipicolinate synthetase (EC 4.2.1.52) AttB-related site argS; lysA Arginyl-tRNA synthetase; Diaminopimelate decarboxylase	X14234	EC 4.1.1.31	Phosphoenolpyruvate carboxylase	Gen. Genet., 212(1):112-119 (1988) Eikmanns, B.J. et al. "The Phosphoenolpyruvate carboxylase gene of Corynebacterium glutamicum: Molecular cloning, nucleotide sequence, and expression," Mol. Gen. Genet., 218(2):330-339 (1989); Lepiniec, L. et al. "Sorghum Phosphoenolpyruvate carboxylase gene family: structure, function
dapA L-2, 3-dihydrodipicolinate synthetase (EC 4.2.1.52) AttB-related site argS; lysA Arginyl-tRNA synthetase; Diaminopimelate decarboxylase	X17313	ſda	Fructose-bisphosphate aldolase	and molecular evolution," Plant. Mol. Biol., 21 (3):487-502 (1993). Von der Osten, C.H. et al. "Molecular cloning, nucleotide sequence and finestructural analysis of the Corynebacterium glutamicum fda gene: structural comparison of C. glutamicum fructose-1, 6-biphosphate aldolase to class I and
argS; lysA Arginyl-tRNA synthetase; Diaminopimelate decarboxylase	A33993	dapA	L-2, 3-dihydrodipicolinate synthetase (EC 4.2.1.52)	Bonnassie, S. et al. "Nucleic sequence of the dapA gene from
argS; lysA Arginyl-tRNA synthetase; Diaminopimelate decarboxylase	A34223		AttB-related site	Cianciotto, N. et al. "DNA sequence homology between att B-related sites of Corynebacterium diphtheriae, Corynebacterium ulcrans, Corynebacterium glutamicum, and the attP site of lambdacorynephage," FEMS. Microbiol,
	A34/40	argS; lysA	Arginyl-tRNA synthetase; Diaminopimelate decarboxylase	Marcel, T. et al. "Nucleotide sequence and organization of the upstream region of the Corynebacterium glutamicum lysA gene," Mol. Microbiol, 4(11):1819-1830 (1990)

		Table 2 (continued)	inied
X33994	trpL; trpE	Putative leader peptide; anthranilate	Heery, D.M. et al. "Nucleotide sequence of the Corynebacterium glutamicum
X56037	thrC	Threonine synthase	TrpE gene," Nucleic Acids Res., 18(23):7138 (1990) Han, K.S. et al. "The molecular structure of the Connection of the Co
X56075	attB-related site	Attachment cite	threonine synthase gene," Mol. Microbiol., 4(10):1693-1702 (1990)
			Corynebacterium diphtheriae, Corynebacterium ulcerans, Corynebacterium glutamicum, and the attP site of lambdacorynephage," FEMS. Microbiol,
X3/226	lysC-alpha; lysC-beta;	Aspartokinase-alpha subunit;	Kalinowski et al "Committee" Kalinowski et al "Committee"
	asd	Aspartokinase-beta subunit; aspartate beta semialdehyde dehydrogenase	from Corynebacterium glutamicum," Mol. Microbiol., 5(5):1197-1204 (1991); Kalinowski, J. et al. "Aspartokinase genes lysC alpha and lysC beta overlan
V£0403			and are adjacent to the aspertate beta-semialdehyde dehydrogenase gene asd in
A39403	gap;pgk; tpi	Glyceraldehyde-3-phosphate; phosphoelycerate kinase: tricearhout as	Eikmanns, B.J. "Identification, sequence analysis, and expression of a
		isomerase	Corynebacterium glutamicum gene cluster encoding the three glycolytic enzymes glyceraldehyde-3-phosphate dehydrogenase, 3-phosphoglycerate kinase, and triosephosphate isomeras," J. Bacteriol., 174(19):6076-6086
X59404	gdh	Glutamate dehydrogenase	Bormann, E.R. et al. "Molecular analysis of the Cormadostarium clusters
V(0010			gdh gene encoding glutamate dehydrogenase," Mol. Microbiol, 6(3):317-326
71007	lysi	L-lysine permease	Seep-Feldhaus, A.H. et al. "Molecular analysis of the Corynebacterium glutamicum lysl gene involved in lysine uptake," Mol. Microbiol. 5(12):2995-
X66078	cop1	Ps1 protein	3005 (1991)
			PS1, one of the two major secreted proteins of Corynebacterium glutamicum: The deduced N-terminal region of PS1 is similar to the Mycobacterium antigen
X66112	glt	Citrate synthase	63 complex, Mol. Microbiol., 6(16):2349-2362 (1992) Eikmanns, B.J. et al. "Cloning sequence, expression and transcriptional
2000			analysis of the Corynebacterium glutanicum gltA gene encoding citrate
A61/3/	dapB	Dihydrodipicolinate reductase	June 25, 1711C 00101., 140:1017-1028 (1994)
X69103	csp2	Surface layer protein PS2	Peyret, J.L. et al. "Characterization of the cspB gene encoding PS2, an ordered surface-layer protein in Corynebacterium glutamicum." Mol. Microbiol
X69104		1S3 related insertion element	9(1):97-109 (1993)
			IS3-related insertion sequence and phylogenetic analysis," Mol. Microbiol.
			14(3):311-301 (1994)

030057		Table 2 (continued	inued)
4660/4	VienA	Isopropylmalate synthase	Patek, M. et al. "Leucine synthesis in Corvnebacterium olutamicum: annume
		•	activities, structure of leuA, and effect of leuA inactivation on lysine
X71489	icd	Isocitrate dehydropenase (NADD+)	Symmests, Appl. Environ. Microbiol., 60(1):133-140 (1994)
			of the Corynebacterium glutamicum icd gene encoding isocitrate
2000			dehydrogenase and biochemical characterization of the enzyme," J. Bacteriol,
X/2833	GDHA	Glutamate dehydrogenase (NADP+)	
X75083,	mtrA	5-methyltryptophan resistance	Heery D.M. et al. "A continue from continue to
A /0384			Corynebacterium glutamicum encoding resistance to 5-methylprophan "
X75085	recA		Biochem. Biophys. Res. Commun, 201(3):1255-1262 (1994)
			Fitzpatrick, R. et al. "Construction and characterization of recA mutant strains
			of Corynebacterium glutamicum and Brevibacterium lactofermentum," Appl.
X75504	aceA; thiX	Partial Isocitrate lyase; ?	Reinscheid D I et al "Characterization of the incidence o
			Corynebacterium glutamicum and hischemical anglusia of the
SLOYLA			Bacteriol., 176(12):3474-3483 (1994)
Cient		A TPase beta-subunit	Ludwig, W. et al. "Phylogenetic relationships of bacteria hased on comparative
			sequence analysis of elongation factor Tu and ATP-synthase beta-subunit
X77034	tuf	Flongation factor T.	genes," Antonie Van Leeuwenhoek, 64:285-305 (1993)
			Ludwig, W. et al. "Phylogenetic relationships of bacteria based on comparative
V77394			sequence analysis of elongation factor Tu and ATP-synthase beta-subunit genes." Anonie Van Leeuwenhoek 64-284, 205 (1002)
+00//	recA		Billman-Jacobe, H. "Nucleotide sequence of a recA gene from
X78491	aceB	Moleto combined	Corynebacterium glutamicum," DNA Seq., 4(6):403-404 (1994)
		intaine syllillase	Reinscheid, D.J. et al. "Malate synthase from Corynebacterium glutamicum
V80620			Pta-ack operon encoding phosphotransacetylase: sequence analysis," Microbiology, 140:3099-3108 (1994)
70000	ANGLES	16S ribosomal RNA	Rainey, F.A. et al. "Phylogenetic analysis of the genera Rhodococcus and
			Norcardia and evidence for the evolutionary origin of the genus Norcardia
			from within the radiation of Rhodococcus species," Microbiol,, 141:523-528
X81191	gluA; gluB; gluC;	Glutamate untake system	(1995)
	GluD		Nonemeyer, W. et al. "Structure of the gluABCD cluster encoding the
X81170	Tack Tack	G	Framinate uplace system of Corynebacterium glutamicum," J. Bacteriol., 177(5):1152-1158 (1995)
\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	appe	Succinyldiaminopimelate desuccinylase	Wehrmann, A. et al. "Analysis of different DNA fragments of
			Corynebacterium glutamicum complementing dapE of Escherichia coli "
			Microbiology, 40:3349-56 (1994)

		Table 2 (continued)	nued)
78 2061	16S rDNA	l6S ribosomal RNA	Ruimy, R. et al. "Phylogeny of the genus Corynebacterium deduced from analyses of small-subunit ribosomal DNA sequences," Int. J. Syst. Bacteriol, 45(4):740-746 (1005)
X82928	asd; lysC	Aspartate-semialdehyde dehydrogenase; ?	Serebrijski, I. et al. "Multicopy suppression by asd gene and osmotic stress-dependent complementation by heterologous proA in proA mutants," J. Bacteriol 177(24):7255-7260 (1905)
X82929	proA	Gamma-glutamyl phosphate reductase	Serebrijski, I. et al. "Multicopy suppression by asd gene and osmotic stress-dependent complementation by heterologous proA in proA mutants," J. Received 1777/2015
X84257	16S rDNA	16S ribosomal RNA	Pascual, C. et al. "Phylogenetic analysis of the genus Corynebacterium based on 16S rRNA gene sequences." Let 1. S. et al.
X85965	aroP; dapE	Aromatic amino acid permease; ?	Wehrmann et al. "Functional analysis of sequences adjacent to dapE of C. glutamicum proline reveals the presence of arop, which encodes the aromatic amino acid transporter." I Beneficial 177700.5001.500
78013 <i>/</i>	argB; argC; argD; argF; argJ	Acetylglutamate kinase; N-acetyl-gamma- glutamyl-phosphate reductase; acetylornithine aminotransferase; ornithine carbamoyltransferase; glutamate N- acetyltransferase	Sakanyan, V. et al. "Genes and enzymes of the acetyl cycle of arginine biosynthesis in Corynebacterium glutamicum: enzyme evolution in the early steps of the arginine pathway," <i>Microbiology</i> , 142:99-108 (1996)
X89084	pta; ackA	Phosphate acetyltransferase; acetate kinase	Reinscheid, D.J. et al. "Cloning, sequence analysis, expression and inactivation of the Corynebacterium glutamicum pta-ack operon encoding
X89850	attB	Attachment site	Le Marrec, C. et al. "Genetic characterization of site-specific integration functions of phi AAU2 infecting "Arthrobacter aureus C70," J. Bacteriol, 178(7):1005, 2004, (1005).
X90356		Promoter fragment F1	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," Microbiology, 147-1707-1300 (1904)
X90357		Promoter fragment F2	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," <i>Microbiology</i> , 147-1207, 1309, 1906,
X90358		Promoter fragment F10	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," <i>Microbiology</i> , 122:1297-1309 (1996)
X90359		Promoter fragment F13	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," <i>Microbiology</i> , 142:1297-1309 (1996)

V00260		Table 2 (continued)	ntinued)
00000		Promoter fragment F22	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," <i>Microbiology</i> , 142-1797-1306 (1906)
X90361		Promoter fragment F34	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," Microbiology, 120, 120, 1200, 12
X90362		Promoter fragment F37	Patek, M. et al. "Promoters from C. glutamicum: cloning, molecular analysis and search for a consensus morte".
X90363 X00324		Promoter fragment F45	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," <i>Microbiology</i> , 142:1297-1309 (1996)
430304		Promoter fragment F64	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," <i>Microbiology</i> , 142:1297-1309 (1996)
A90303		Promoter fragment F75	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," <i>Microbiology</i> , 142:1297-1309 (1996)
X90367		Promoter fragment PF101	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," <i>Microbiology</i> , 142:1297-1309 (1996)
ayt.06X		Promoter tragment PF104	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," <i>Microbiology</i> , 142:1297-1309 (1996)
900000		Promoter fragment PF109	Patek, M. et al. "Promoters from Corynebacterium glutamicum: cloning, molecular analysis and search for a consensus motif," <i>Microbiology</i> , 142:1297-1309 (1996)
A95515	amt	Ammonium transport system	Siewe, R.M. et al. "Functional and genetic characterization of the (methyl) ammonium uptake carrier of Corynebacterium glutamicum," J. Biol. Chem., 271(10):5308-5403 (1905)
X93514	betP	Glycine betaine transport system	Peter, H. et al. "Isolation, characterization, and expression of the Corynebacterium glutamicum betP gene, encoding the transport system for the
X95649	orf4		Patek, M. et al. "Identification and transcriptional analysis of the dapB-ORF2-dapA-ORF4 operon of Corynebacterium glutamicum, encoding two enzymes
X96471	lysE; lysG	Lysine exporter protein; Lysine export regulator protein	Vrljic, M. et al. "A new type of transporter with a new type of cellular function: L-lysine export from Corynebacterium glutamicum," Mol.
			Microbiol, 22(5):815-826 (1996)

		Table 2 (continued)	(panul
V02500			
A96380	panB; panC; xyIB	3-methyl-2-oxobutanoate hydroxymethyltransferase; pantoate-beta- alanine ligase; xylulokinase	Sahm, H. et al. "D-pantothenate synthesis in Corynebacterium glutamicum and use of panBC and genes encoding L-valine synthesis for D-pantothenate overproduction," <i>Appl. Environ. Microbiol.</i> , 65(5):1973-1979 (1999)
X96962		Insertion sequence IS1207 and transmisses	
X99289		Elongation factor P	Ramos, A. et al. "Cloning, sequencing and expression of the gene encoding elongation factor P in the amino-acid producer Brevibacterium lactofermentum
Y00140	thrB	Homoserine kinase	Mateos, L.M. et al. "Nucleotide sequence of the homoserine kinase (thrB) gene of the Bravilacterium loctoferm."
Y00151	db	Meso-diaminopimelate D-dehydrogenase (EC 1.4.1.16)	Ishino, S. et al. "Nucleotide sequence of the meso-diaminopimelate D-dehydrogenase gene from Corynebacterium glutamicum," Nucleic Acids Res.,
Y00476	thrA	Homoserine dehydrogenase	Mateos, L.M. et al. "Nucleotide sequence of the homoserine dehydrogenase (thrA) gene of the Brevibacterium lactofermentum," Nucleic Acids Res.,
Y00546	hom; thrB	Homoserine dehydrogenase; homoserine kinase	Peoples, O.P. et al. "Nucleotide sequence and fine structural analysis of the Corynebacterium glutamicum hom-thrB operon," Mol. Microbiol., 2(1):63-72.
Y08964	murC; ftsQ/divD; ftsZ	UPD-N-acetylmuramate-alanine ligase; division initiation protein or cell division protein: cell division protein	Honrubia, M.P. et al. "Identification, characterization, and chromosomal organization of the fisZ gene from Brevibacterium lactofermentum," Mol. Gen.
Y09163	putP	High affinity proline transport system	Peter, H. et al. "Isolation of the putP gene of Corynebacterium glutamicumproline and characterization of a low-affinity uptake system for
Y09548	pyc	Pyruvate carboxylase,	Peters-Wendisch, P.G. et al. "Pyruvate carboxylase from Corynebacterium glutamicum: characterization, expression and inactivation of the pyc gene,"
Y09578	leuB	3-isopropylmalate dehydrogenase	Patek, M. et al. "Analysis of the leuß gene from Corynebacterium glutamicum." Appl. Microhiol. Riotechnol. 50(1):43, 47 (1000)
7/4711		Attachment site bacteriophage Phi-16	Moreau, S. et al. "Site-specific integration of corynephage Phi-16: The
Y12537	ргоР	Proline/ectoine uptake system protein	Peter, H. et al. "Corynebacterium glutamicum is equipped with four secondary carriers for compatible solutes: Identification, sequencing, and characterization of the proline/ectoine uptake system, ProP, and the ectoine/proline/glycine betaine carrier Ecto".
			Octaine Califer, Ectr., J. Bacteriol., 180(22):6005-6012 (1998)

Jakoby, M. et al. "Isolation of Corvnebacterium olistamicum of A
BUSIN WILLY INTERIOR STREET
encoding glutamine synthetase I," FEMS Microbiol. Lett., 154(1):81-88 (1997)
Attachment site Corynephage 304L Moreau, S. et al. "Analysis of the integration functions of & phi 3041 . An
Arginyl-tRNA synthetase; diaminopimelate Oguiza, J.A. et al. "A gene encoding arginyl-tRNA synthetase is located in the upstream region of the lysA gene in Brevibacterium lactofermentum: Regulation of areS-lysA chister avages." Virology, 255(1):150-159 (1999) Regulation of areS-lysA chister avages."
Pisabarro, A. et al. "A cluster of three genes (dapA, orf2, and dapB) of Brevibacterium lactofermentum encodes dihydrodipicolinate reductase, and a third bolyneptide of inhancum function."
(1993) Malumbres, M. et al. "Analysis and expression of the throught."
threonine synthase," Appl. Environ. Microbiol., 60(7)2209-2219 (1994)
Oguiza, J.A. et al "Multiple sigma factor genes in Brevibacterium lactofermentum: Characterization of sigA and sigB," J. Bacteriol 178(2).550
vity UDP-galactose 4- Oguiza, J.A. et al "The galE gene encoding the UDP-galactose 4-epimerase of Brevibacterium lactofermentum is coupled transcriptionally to the dmdp.
gene," Gene, 177:103-107 (1996) Oguiza, J.A. et al "Multiple sigma factor genes in Brevibacterium lactofermentum: Characterization of sigA and sigB," J. Bacteriol, 178(2):550.
Correia, A. et al. "Cloning and characterization of an IS-like element present in the genome of Brevibacterium lactofermentum ATCC 13869," Gene, 170(1)-91-04 (1995)
the published version. It is believed that the published version relied on an incorrect start codon, and thus represents only a fragment of the actual coding region.
sequence ct start co

TABLE 3: Corynebacterium and Brevibacterium Strains Which May be Used in the Practice of the Invention

Genus 📜 📻		ATCE	EERN	INRR	CEC	I NGIMB	ECRC#	NOTE	Dev
Brevibacterium	ammoniagenes	21054			37. 33		200	ACTO	MSM.
Brevibacterium	ammoniagenes	19350		 	 		 		
Brevibacterium	ammoniagenes	19351		 		 		 	<u> </u>
Brevibacterium	ammoniagenes	19352		 	+	 -			ļ
Brevibacterium	ammoniagenes	19353		 	+-	+			
Brevibacterium	ammoniagenes	19354		 	+	+			
Brevibacterium	ammoniagenes	19355		 		 			
Brevibacterium	ammoniagenes	19356		 	╁	+			
Brevibacterium	ammoniagenes	21055				+			
Brevibacterium	ammoniagenes	21077			+	+			<u> </u>
Brevibacterium	ammoniagenes	21553			+	+			
Brevibacterium	ammoniagenes	21580		 -	 	+			
Brevibacterium	ammoniagenes	39101			+	+			
Brevibacterium	butanicum	21196			+	+			
Brevibacterium	divaricatum	21792	P928		 	+			
Brevibacterium	flavum	21474			 	+			
Brevibacterium	flavum	21129			 	 		 -	
Brevibacterium	flavum	21518			 	 			
Brevibacterium	flavum			B11474	 	 			
Brevibacterium	flavum			B11472	 	╂╾╌╾┼			
Brevibacterium	flavum	21127				 			
Brevibacterium	flavum	21128			 				
Brevibacterium	flavum	21427				 			
Brevibacterium	flavum	21475							
Brevibacterium	flavum	21517							
revibacterium	flavum	21528							
revibacterium	flavum	21529							
revibacterium	flavum			B11477				-+	
revibacterium	flavum			B11478					
revibacterium	flavum	21127							
revibacterium	flavum			B11474					
	healii	15527							
revibacterium	ketoglutamicum	21004							
	ketoglutamicum	21089							
	ketosoreductum	21914							
	lactofermentum				70		 -	 -	
	lactofermentum				74				
	lactofermentum				77				
	lactofermentum	21798							
	lactofermentum	21799			+			-+	
	lactofermentum	21800							
	actofermentum	21801			- 				$-\!\!\!\!-\!\!\!\!\!-$
	actofermentum		В	11470					
evibacterium	actofermentum			11471					

Describeration	Species N. V.	BATEC	FERM	NRRL	CECT	NCIMB	*CBS*	NCTE	DSMZ
Die vioaetei iaili	nactotermentum	21086			1.		37.0	1 2 3	.7
Brevibacterium	lactofermentum	21420							
Brevibacterium	lactofermentum	21086							
Brevibacterium	lactofermentum	31269						 	
Brevibacterium	linens	9174						<u> </u>	-
Brevibacterium	linens	19391						<u> </u>	
Brevibacterium	linens	8377							
Brevibacterium	paraffinolyticum					11160			
Brevibacterium	spec.						717.73		
Brevibacterium	spec.						717.73		
Brevibacterium	spec.	14604							
Brevibacterium	spec.	21860							
Brevibacterium	spec.	21864							
Brevibacterium	spec.	21865							
Brevibacterium	spec.	21866							
Brevibacterium	spec.	19240			 +				
Corynebacterium	acetoacidophilum	21476							
Corynebacterium	acetoacidophilum	13870							
Corynebacterium	acetoglutamicum			B11473					
Corynebacterium	acetoglutamicum	+		B11475					
Corynebacterium	acetoglutamicum	15806	 -	0114/3					
Corynebacterium	acetoglutamicum	21491							
Corynebacterium	acetoglutamicum	31270							
Corynebacterium	acetophilum			B3671					
Corynebacterium	ammoniagenes	6872		B30/1			-		
Corynebacterium	ammoniagenes	15511						2399	
Corynebacterium	fujiokense	21496							
Corynebacterium	glutamicum	14067							
Corynebacterium	glutamicum	39137							
Corynebacterium	glutamicum	21254							
orynebacterium	glutamicum	21255							
	glutamicum	31830							
	glutamicum	13032							
	glutamicum	14305						T	
	glutamicum								
	glutamicum	15455							
	glutamicum	13058							
	glutamicum	13059							
	glutamicum	13060							
	glutamicum	21492							
	glutamicum	21513							
		21526							
	glutamicum	21543							
	glutamicum	13287							
		21851							
		21253							
		21514							
		21516							
rynebacterium g	lutamicum	21299							 -

Central			THE PASS	- Amber	CRAT	ENTOTE OF	li conor		
Corynebacterium	PROBLEM TO	ALCC	ET PIKOV	AKKE	CEGI	uciur	EGRZ 養	Vere	DSMZ
Corynebacterium	glutamicum	21300			ļ				
Corynebacterium	glutamicum	39684							
Corynebacterium	glutamicum	21488		ļ	ļ				
Corynebacterium	glutamicum	21649	ļ	<u>_</u>				<u> </u>	
Corynebacterium	glutamicum	21650							
Corynebacterium	glutamicum	19223							
Corynebacterium	glutamicum	13869			L				
	glutamicum	21157							
Corynebacterium	glutamicum	21158							
Corynebacterium	glutamicum	21159							
Corynebacterium	glutamicum	21355							
Corynebacterium	glutamicum	31808							
Corynebacterium	glutamicum	21674							
Corynebacterium	glutamicum	21562							
Corynebacterium	glutamicum	21563							
Corynebacterium	glutamicum	21564			I				
Corynebacterium	glutamicum	21565	l						
Corynebacterium	glutamicum	21566							
Corynebacterium	glutamicum	21567							
Corynebacterium	glutamicum	21568							
Corynebacterium	glutamicum	21569							
Corynebacterium	glutamicum	21570							
Corynebacterium	glutamicum	21571							
Corynebacterium	glutamicum	21572							
Corynebacterium	glutamicum	21573							
Corynebacterium	glutamicum	21579							
Corynebacterium	glutamicum	19049							
Corynebacterium	glutamicum	19050							
Corynebacterium	glutamicum	19051							
Corynebacterium	glutamicum	19052							
Corynebacterium	glutamicum	19053							
Corynebacterium	glutamicum	19054							
Corynebacterium	glutamicum	19055							
Corynebacterium	glutamicum	19056							
Corynebacterium	glutamicum	19057							
Corynebacterium	glutamicum	19058							
Corynebacterium	glutamicum	19059							
	glutamicum	19060							
	glutamicum	19185							
	glutamicum	13286							
	glutamicum	21515							
	glutamicum	21527							$\overline{}$
	glutamicum	21544							
	glutamicum	21492							
	glutamicum			B8183				 	
	glutamicum	*		B8182					
	glutamicum		I	312416					
Corynebacterium	glutamicum		- t-	312417					

Central Falls Etc.	Species 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	TATCC	FERM	NRRE	CECT	NGIME	FORCE	NCTO	I DON'T
	glutamicum			B12418	445.	1,031,110	, C155	MCIG	DOW
Corynebacterium	glutamicum			B11476					
Corynebacterium	glutamicum	21608		511470					
Corynebacterium	lilium		P973						
Corynebacterium	nitrilophilus	21419	1773			11504			
Corynebacterium	spec.		P4445			11594			
Corynebacterium	spec.		P4446						
Corynebacterium	spec.	31088	1 1110						
Corynebacterium	spec.	31089							
Corynebacterium	spec.	31090							
Corynebacterium	spec.	31090							
Corynebacterium	spec.	31090							
	spec.	15954							
	spec.	21857							20145
\	spec.	21862							
	spec.	21863							

ATCC: American Type Culture Collection, Rockville, MD, USA

FERM: Fermentation Research Institute, Chiba, Japan

NRRL: ARS Culture Collection, Northern Regional Research Laboratory, Peoria, IL, USA

CECT: Coleccion Espanola de Cultivos Tipo, Valencia, Spain

NCIMB: National Collection of Industrial and Marine Bacteria Ltd., Aberdeen, UK

CBS: Centraalbureau voor Schimmelcultures, Baarn, NL

NCTC: National Collection of Type Cultures, London, UK

DSMZ: Deutsche Sammlung von Mikroorganismen und Zellkulturen, Braunschweig, Germany

For reference see Sugawara, H. et al. (1993) World directory of collections of cultures of microorganisms: Bacteria, fungi and yeasts (4th edn), World federation for culture collections world data center on microorganisms, Saimata, Japen.

TABLE 4: ALIGNMENT RESULTS Length Accession Name of Genbank Hit

	** \	J 01/00804	,												PC'	Г/IB00/009	22
	Date of	<u>Deposit</u> 5-Jun-99	18-DEC-1997	6-Feb-97 18,DEC-1997	16-OCT-1998 13-OCT-1999	13-OCT-1999		12-Jan-99	-2-Apr-99 -2-Aug-99 -			29-MAR-1996	30-MAR-1998	30.MAD 1000			
	% homology Date of	(GAP) 39,080	-						30,313 1 44,159 2			40,420 2	40,420	40 420			
	Source of Genbank Hit	Homo sapiens			lanogaster	Drosophila melanogaster 36,589			Coefficolor							pelicolor	la melanogaster 3
	Source	Ното	Homo sapiens	Homo 8	nomo sapiens Drosophila mel	Drosopt	i					Homo sapiens	Homo sapiens	Homo sapiens	Mycobacterium	tuberculosis Escherichia coli Escherichia coli Streptomyces co	A3(2) Drosophi
Length Accession Name of Genhank His		6 Homo sapiens clone NH0501G22, *** SEQUENCING IN PROGRESS *** 3 unordered pieces.	Homo sapiens CAGH44 mRNA, partial cds. B.nigra DNA for tRNA like gene.				1.5 unordered pieces. Streptomyces coelicolor cosmid 9C7			(gspG), general secretory pathway protein H (gspH), general secretory pathway protein G protein I (gspH), general secretory pathway protein J (gspH), general secretory pathway protein J (gspJ), general secretory pathway protein J (gspJ), general secretory	secretory pathway protein M (gspM), and general secretory pathway protein N (gspN) genes, complete cds, and unknown genes.	zacoguz.s1 Soares fetal liver spleen 1NFLS Homo sapiens cDNA clone IMAGE:297458 3', mRNA sequence.	SHGC-56832 Human Homo sapiens STS genomic, sequence tagged site.	SHGC-56832 Human Homo sapiens STS genomic, sequence tagged site.	Mycobacterium tuberculosis H37Rv complete genome; segment 133/162.	Escherichia coli genomic sequence of minutes 9 to 12. Escherichia coli K-12 MG1655 section 55 of 400 of the complete genome. Streptomyces coelicolor cosmid F43A.	A3(2) of Drosophila melanogaster genome survey sequence SP6 end of BAC BACN14G08 Drosophila melanogaster 37,573 sequence.
th Accessio		185001 AC007366	U80741 X89901	080741 AQ163721	171979 AC007054	171979 AC007054	AL035161	AL049628	AF110185		10000	/90.09N	G37084	G37084	283866	136742 U82598 12003 AE000165 35437 AL096837	AL105910
Lengt				388 388			31360	38532	70507		26	ţ	38 4	384	31859	136742 12003 35437	1036
length Genbank Hit		GB_HTG2:AC007366	GB_PR3:HSU80741 GB_PL1:BNDNATRNA GB_BD3:HSU80744	GB_GSS9:AQ163721	GB_HTG4:AC007054	GB_HTG4:AC007054	GB_BA1:SC9C7	GB_BA1:SCE94	69101110130		GR ESTE NR0167		GB_S1S:G3/084	GB_STS:G37084	GB_BA1:MTCY22D7	GB_BA1:ECU82598 GB_BA2:AE000165 GB_BA1:SCF43A	GB_GSS2:CNS015U4 1036
ID # length	(IN)	ка00062 1521	rxa00084 948	rxa00109 735			rxa00215 1449				1299 rxa00289				ra00404 2439	xa00479 2313	

	GB_PR3:HSA494016	50502	AL117328	Human DA				
xa00497 420	GB BA1-MTCV78	4000			Homo sapiens	36,475	23-Nov-99	W
			5//165	Mycobacterium tuberculosis H37Rv complete genome; segment 145/162.	Mycobacterium	40.250) 0
	GB_BA2:AF079544 GB_BA1:MTGROEOP	817	AF079544 X60350	Mycobacterium avium GroESL operon, partial sequence. M.tuberculosis groE gene for KCS and 10 km, and decidents	tuberculosis Mycobacterium avium	64,439	16-Aug-98	1/0080
rxa00575				Since of the products.	Mycobacterium tuberculosis	62,857	23-Apr-92)4
rxa00599 510	GB_GSS10:AQ199703 439	3 439	AQ199703	RPCI11-46013.TJ RPCI-11 Home sapiens genomic clane BPCI 11 46012				
	GB_PR2:AC002127	144165	144165 AC002127	genomic survey sequence. Human BAC clone RG305H12 from 7q21, complete sequence.	Homo sapiens	42,657	20-Apr-99	
	GB_STS:G51234	430	G51234		rionio sapiens	37,052	27-MAY-1997	
. rxa00600 1221	GB_BA1:MTCY441	35187	Z80225	STICC-50/08 Human Homo sapiens STS genomic, sequence tagged site. Mycobacterium tuberculosis H37Rv complete genome: segment 118/162	Homo sapiens	42,657	25-Jun-99	
	GB_BA1:MSGY223	42061	AD000019	Mycobacterium hiberculosis socioses &	tuberculosis	56,183	18-Jun-98	
				Sequelice Itom Glone y223.	Mycobacterium	37,217	10-DFC-1996	
rxa00605 1603	GB_BA1:BSUB0014 GB_BA2:AF069070	213420 2776	213420 Z99117 2776 AF069070	Bacillus subtilis complete genome (section 14 of 21): from 2599451 to 2812870. Endosymbiont of Onchocerca volvulus catalase gene, complete cds.	tuberculosis Bacillus subtilis endosymbion of	36,553	26-Nov-97	-7
	GB_BA1:OVCAT	1845	X82176	Onchocerca volvulus endobacterial mRNA for contring	Onchocerca volvulus	35,396	25-Nov-98	9-
					endosymbiont of	55,396	26-Nov-98'	
rxa00648 1533	GB_BA1:SC2G5	38404	AL035478	Streptomyces coelicolor cosmid 2G5.	Onchocerca volvulus		3	
	de_n131.n3/4016	169401	169401 AL110119	Homo sapiens chromosome 21 clone RPCIP70401674 map 21o21 ***	Streptomyces coelicolor	39,530	11-Jun-99	
	GB_HTG1:HS74016	169401	169401 AL110119	SEQUENCING IN PROGRESS ***, in unordered pieces.	rono sapiens	36,327	27-Aug-99	
	GB_HTG1:HS74016	169401	169401 Al 110119	SEQUENCING IN PROGRESS *** in unordered pieces.	Homo sapiens	36,327	27-Aug-99	
xa00764 1239		609		FOUR SEQUENCING IN PROGRESS ***, in unordered pieces.	Homo sapiens	35,119	27-Aug-99	
				CS120745U (Omato ovary, TAMU Lycopersicon esculentum cDNA clone cLED31K22, mRNA sequence.	Lycopersicon esculentum 34,323	1 34,323	27-Jul-99	
				Pseudomonas aeruginosa YafE (yafE), LeuB (leuB), Asd (asd), FimV (fimV), and HisT (hisT) genes, complete cds; TrpF (trpF) gene, partial cds; and internate	Pseudomonas	35,895	23-Jun-98	PC
			U932/4	Pseudomonas aeruginosa YafE (yafE), LeuB (leuB), Asd (asd), FimV (fimV), and HisT (hisT) oenes complete and	Pseudomonas	41.417	23. hin.08	T/I
rxa00803 1353	GB_IN2:CELH34C03 CB HTG2-AC00700E				aeruginosa		06-106-04	B 00
		100/27		ne PAC 754F23, *** SEQUENCING IN	caenomabditis elegans Homo sapiens	34,152 37,472	28-OCT-1998 24- lun-99)/00
	GB_HTG2:AC007905	100722 /	100722 AC007905 P	done PAC 754F23, *** SEQUENCING IN	Homo sapiens	37,472	24-Jun-99	922

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rxa00810 324	GB_BA1:MTY15C10	33050	295436	Table 4 (continued) Mycobacterium tuberculosis H37Rv complete genome; segment 154/162.	Mycobacterium	. 20	
rxa00829 2463	GB_BA1:MLCB2548 GB_BA1:ECOUW76 GB_BA1:SC5C7 GB_BA1:SC5F2A	38916 225419 41906 40105	AL023093 9 U00039 AL031515 AL049587		Tuberculosis Mycobacterium leprae Escherichia coli Streptomyces coelicolor Streptomyces		1/Jun-98 27-Aug-99 7-Nov-96 7-Sep-98
rxa00843 468	GB_BA1:STMDRRC GB_BA1:MTCY9C4	3374 15916	L76359 Z77250	Streptomyces peucetius daunorubicin resistance protein (drrC) gene, complete Mycobacterium tuberculosis H37Rv complete genome: segment 113/162	Streptomyces peucetius		24-MAY-1999 24-DEC-1996
	GB_BA1:MTCY9C4	15916	277250	Mycobacterium tuberculosis H37Rv complete genome; segment 113/162.	tuberculosis Mycobacterium tuberculosis	37,773	17-Jun-98 17-Jun-98
rxa00858 568	GB_BA1:SCC54 GB_EST18:N96610	30753 547	AL035591 N96610	Streptomyces coelicolor cosmid C54.	Streptomyces coelicolor	r 39.602	11-lin-00
гха00886 1269	GB_EST18:T45493 GB_BA1:SYCSLLLH GB_BA1:SCDNA.1	436 132106 5611		8756 Lambda-PRL2 Arabidopsis thaliana CDNA clone F10G3T7, mRNA Synechocystis sp. PCC6803 complete genome, 25/27, 3138604-3270709	Arabidopsis thaliana Arabidopsis thaliana Synachocystic so		5-Jan-98 4-Aug-98
	GB_BA1:STMDNAK	4648	L46700	Streptomyces coelicolor (strain A3(2)) dnaK operon encoding molecular	Streptomyces coelicolor Streptomyces coelicolor	49,744	13-Feb-99 21-Nov-96 22 Mar. 66
ra00900 975	GB_BA2:ECOUW67_0 110000 U18997 GB_BA2:ECOUW67_0 110000 U18997	0 110000	U18997 U18997		Escherichia coli		U18997 8
xa00901 537	GB_HTG3:AC010757	10516 175571	AE000393 AC010757	1283 of 400 of the complete genome. 128_C_18 map 18, *** SEQUENCING IN	Escherichia coli Escherichia coli Homo escisso	37,759	U18997 12-Nov-98
	GB_HTG3:AC010757	175571	175571 AC010757		Homo sapiens	34,857	22-Sep-99
25 JOSEP	GB_HTG3:AC011283	87295	AC011283		Homo sapiens	35,448	07-OCT-1999
907 TORONS	GB_PL2:AC007887	512 159434	512 AJ245664 159434 AC007887	ial mRNA for ATP-citrate lyase (ACL gene). Se for Arabidopsis thaliana BAC F15O4 from chromosome I,	Gallus gailus Arabidopsis thaliana	37,538 37,600	28-Sep-99 04-OCT-1999
rxa00995 864	GB_GSS1:CNS00RNW542 GB_EST29:A1553951 450		AL087338 Al553951	Arabidopsis thaliana genome survey sequence T7 end of BAC F14D7 of IGF library from strain Columbia of Arabidopsis thaliana, genomic survey sequence.	Arabidopsis thaliana	41,264	28-Jun-99
				3' similar to gb:X02067 H.sapiens mRNA for 7SL RNA pseudogene (HUMAN); mRNA sequence.	Homo sapiens	42,627	13-Apr-99
	GB_PR3:AC003029 GB_BA1:EAY14603	139166 ,	139166 AC003029	well Park Cancer	Homo sapiens	38,915	17-Sep-98
rxa00996 864	.42	_	2 2	Criwina amylovora snA, snE, snB, snD, snM and snR genes. Archaeoglobus fulgidus section 106 of 172 of the complete genome. AVO18764 Mus musculus 18-day embryo C57BL/6J Mus musculus cDNA clone M1190006M16, mRNA sequence.	Erwinia amylovora Archaeoglobus fulgidus Mus musculus	37,694 41,078 39,669	6-Jan-98 15-DEC-1997 28-Aug-99

,	W(O 01/008	04						-81	_						P	CT	TB0 0	/0092	2	
	10-OCT-1997	12-Jul-97 19-DEC-1996	12-Sep-96	21-MAY-1999	04-DEC-1999	19-Jul-99	2-Aug-97		7-Feb-99	07-DEC-1999	07-DEC-1999	10-Feb-99 03-DEC-1999	03.DEC_1000	08-OCT-1999	08-OCT-1999	24.48.00		19-Aug-99		14-Aug-98 AC011500	23-Sep-99
	44,385	46,629 38,677	58,696	37,651	36,011	38,640	39,344		32,205	106'30	38,476	42,925 36,825	36,825	35,794	40,625	35 014	17,697	17,697	38,195	36,446	35,764
	Arabidopsis thaliana	Coturnix coturnix Mus musculus	Mus musculus	Homo sapiens	d Homo sapiens	Homo sapiens	Caenorhabditis elegans Caenorhabditis elegans	arilled arilles	Homo saniens			Ipomoea nii Homo sapiens	Homo sapiens	Caenorhabditis elegans	Caenorhabditis elegans Mus musculus	Neisseria meningitidis	Plasmodium falciparum	Plasmodium falciparum	Homo sapiens	Homo sapiens	Homo sapiens
F19E16TF IGF Arabidopsis thaliana cenomic clone F19E16TF	sednence.	 Coturnix coturnix arylalkylamine N-acetyltransferase mRNA, partial cds. ms50c09.r1 Life Tech mouse embryo 13 5dpc 10666014 Mus musculus cDNA clone IMAGE:614992 5' similar to SW:NEST_RAT P21263 NESTIN: , mRNA enginees 	mf64g11.r1 Soares mouse embryo NbME13.5 14.5 Mus musculus cDNA clone IMAGE:419108 5' similar to SW:NEST_RAT P21263 NESTIN. [1];, mRNA sequence	_			Caenorhabditis elegans cosmid C13D9.	Chicken novel maf-related gene mafG encoding bZip nuclear protein MafG			unordered pieces. Pharbitis nil mRNA for Dharbitis nil Commit ill.	Homo sapiens chromosome 6 clone RP3-402N21 map p21.1-21.31, ************************************	Homo sapiens chromosome 6 clone RP3-402N21 map p21.1-21.31, ***SEOI IEMOING IN DOCUMENT TO THE PROPERTY OF THE	Caenorhabditis elegans cosmid F18A12. Caenorhabditis elegans cosmid F18A12. Caenorhabditis elegans cosmid F18A12.	Mouse cystic fibrosis transmembrane conductance regulator (CFTR) mRNA,	Neisseria meningitidis chloramphenicol acetyltransferase gene, complete cds.	Progress ***, in unordered pieces.	Plasmodium falciparum chromosome 13 strain 3D7, *** SEQUENCING IN PROGRESS ***, in unordered pieces.	Homo sapiens chromosome 17, clone hRPK 214_O_1, complete sequence. Homo sapiens chromosome 17, clone hRPK 214_O_1, complete sequence.	Homo sapiens chromosome 19 clone CIT978SKB_60E11, *** SEQUENCING IN PROGRESS ***, 246 unordered pieces.	Homo sapiens clone 6_L_24, LOW-PASS SEQUENCE SAMPLING.
B24189		AF007068 AA166324	W89968	AQ381423	206121 AC010901	AQ746932	AF016420 AF016420	D28601	146468 AC010765	146468 AC010765	D45425	AL049553	AL049553	AF016688 AF016688	M60493	AF031037 Al 109815			166687 AC005224 166687 AC005224		AC010831
377		356 1 514	4	3 579	206121	837	43487 43487	1316	146468	146468	362	170302	170302	29784 29784	6304	1472 80518		81008	166687 166687	69000	70233
GB_GSS3:B24189		GB_EST10:AA166324	GB_EST7:W89968	GB_GSS12:AQ381423 579	GB_HTG6:AC010901	GB_GSS5:AQ746932	GB_IN1:CELC13D9	GB_OV:CHKMAFG1	GB_HTG6:AC010765	GB_HTG6:AC010765	GB_PL1:PHNPNGLP	GB_HTG2:HSJ402N21 170302 AL049553	GB_HTG2:HSJ402N21 170302 AL049553	GB_IN2:CELF18A12 GB_IN2:CELF18A12	GB_RO:MUSMCFTR	GB_BA2:AF031037 1472 GB_HTG1:PFMAL13PA80518	SCOTT AND CONTRACT	ξ 2	GB_PR3:AC005224 166687 GB_PR3:AC005224 166687 GB_HTG3:AC011500 1200854		158010831u-25
	CX=01010 1242	767		rxa01051 732		0010E2 422	701 700	rxa01053 543			xa01054 612			rxa01217 723		rxa01320 1770		CKB01345 1575		101 TO11	

WO 01/00804			-82-			PCT/IB00/0	00922
23-Sep-99 30-Sep-98 1-Aug-99 3-Sep-99	26-Nov-97 2-Aug-99 2-Aug-99	14-Jul-99 14-Jul-99		41-DEC-1998 9-Apr-97 23-Aug-99	23;Aug-99	13-Jul-99 04-OCT-1999 22-Aug-99	22-Aug-99 8-Sep-99 26-Apr-93
35,764 40,778 41,234 er 39,432 er 39,432	38,201 er 38,302 er 38,302	37,873 40,220 42,960		99,933 11136,111	r 36,111	36,419 36,317 35,303	35,303 35,409 35,189
Homo sapiens 35,764 Homo sapiens 40,778 Homo sapiens 41,234 Drosophila melanogaster 39,432	Bacillus subtilis 38,201 Drosophila melanogaster 38,302 82 Drosophila melanogaster 38,302	Homo sapiens Homo sapiens Ralstonia eutropha	Vogesella indigofera Caenorhabditis elegans Homo saniens	Corynebacterium 99,933 glutamicum Drosophila melanogaster 36,111	Drosophila melanogaster 36,111 Daucus carota	Homo sapiens Homo sapiens Homo sapiens	Homo sapiens Homo sapiens Escherichia coli
Homo sapien Homo sapien Homo sapien Drosophila m 02. G.21 map B9 unordered Drosophila m	olete genome (section 15 of 21): from 2795131 to 3013540, ister chromosome 2 clone BACR13J10 (D924) RPCI-98 3 strain y; cn bw sp, *** SEQUENCING IN PROGRESS***, ister chromosome 2 clone BACR13J10 (D924) RPCI-98 5 strain y; cn bw sp, *** SEQUENCING IN PROGRESS ****	82 unordered pieces. Homo sapiens 14q32 Jagged2 gene, complete cds; and unknown gene. Homo sapiens 14q32 Jagged2 gene, complete cds; and unknown gene. Alcaligenes eutrophus genes for ureases, ureD1, ureD2, ureA, ureB, and ORF1,	Vogesella indigofera indigoidine biosynthesis regulatory locus, complete Caenorhabditis elegans cosmid M04D8, complete sequence.	mKNA sequence. Corynebacterium glutamicum multidrug resistance protein (cmr) gene, complete cds. Drosophila melanogaster chromosome 3 clone BACR09F18 (D812) RPCI-98 09.F. 18 map 98D-98D strain y, cn bw sp, *** SEQUENCING IN PROGRESS ****	Tub unordered pieces. Drosophila melanogaster chromosome 3 clone BACR09F18 (D812) RPCI-98 09.F.18 map 98D-98D strain y; cn bw sp. *** SEQUENCING IN PROGRESS***. 109 unordere ⁸ t pieces. Daucus carota mRNA for citrate synthase, complete cds.	Homo sapiens endothelial nitric oxide synthase gene, complete cds. Homo sapiens clone NH0166D23, *** SEQUENCING IN PROGRESS ***, 7 unordered pieces. Homo sapiens chromosome 9 clone 30_C_23 map 9, *** SEQUENCING IN PROGRESS *** 20 inordered signal.	Homo sapiens chromosome 9 clone 30_C_23 map 9, *** SEQUENCING IN PROGRESS ***, 20 unordered pieces. Homo sapiens clone 115_I_23, LOW-PASS SEQUENCE SAMPLING. E.coli protein p7 (neu C) gene, complete cds.
70233 AC010831 38400 AC004058 246546 AF152365 121256 AC007890 121256 AC007890	218410 Z99118 107439 AC008260 107439 AC008260	148083 AF111170 148083 AF111170 5740 Y13732	AF088857 Z32682 AI281910	2531 U43535 114735 AC009213	AC009213 AB017159	154754 AC011234 124337 AC009450	
	21841 10743 10743	148083 148083 6740	2908 21552 276	2531	114735	154754 154754 124337	124337 134724 1676
GB_HTG3:AC010831 GB_PR3:AC004058 GB_PR4:AF152365 GB_HTG3:AC007890	GB_BA1:BSUB0015 218410 Z99118 GB_HTG2:AC008260 107439 AC008260 GB_HTG2:AC008260 107439 AC008260	GB_PR4:AF111170 GB_PR4:AF111170 GB_BA1:AEY13732	GB_BA2:AF088857 GB_IN1:CEM04D8 GB_EST25:AI281910	GB_BA1:CGU43535 GB_HTG3:AC009213	GB_HTG3:AC009213 114735 AC009213 GB_PL1:AB017159 1859 AB017159	GB_PR1:HUMGNOS4823142 GB_HTG3:AC011234 154754 GB_HTG3:AC009450 124337	GB_HTG3:AC009450 124337 AC009450 GB_HTG3:AC009919 134724 AC009919 GB_BA1:ECONEUC 1676 M84026
ra01408 324	rxa01524 1566	rxa01578 1510	אפט1616 1605	гха01666 1500	אמסוו674 1017	ка01873 1359	ка01922 1275

	GR HTG2.AC007863	116700 4 000201	Table 4 (continued)		
	30 000 TO 11 000	11628U ACUU/85;	03.L.2 map 96B-96C strain y; on bw sp, *** SEQUENCING IN PROGRESS **** sn	Drosophila melanogaster 34,365	2-Aug-99
	GR HTG2.AC007863	446000 4 000000	unordered pieces.		
	10000V:30 III	11026U ACUU/85	CC_11 CZ. CCC 830 11020V ACUU/833 Drosophila melanogaster chromosome 3 clone BACR03102 (D766) RPCI-98	Orosonbila melanometer 24 per	
			03.L.2 map 96B-96C strain y; on bw sp, *** SEQUENCING IN PROGRESS***, 80		2-Aug-99
rxa01936 1395	ка01936 1395 GB_HTG4:AC010037 166249 AC010037	166249 AC010037			
	GB HTG4.AC010037	188340 A CO.	SEQUENCING IN PROGRESS *** 52 unordered pieces.	Drosophila melanogaster 38,534	16-OCT-1999
		15051903 ACG10031	SEQUENCING STATE S	Drosophila melanogaster 38,534	16-OCT-1999
xa01984 420	GB_PR4:AC005552 GB_PR1:HS169C8F	167228 AC005552	Homo sapiens chromosome 17, clone hRPK.212_E_8, complete sequence.	Homo sapiens	90
			n.sapiens CpG island DNA genomic Mse1 fragment, clone 169c8, forward read cog169c8 ft1a		18-OCT-1995
	GB_BA1:SERATTBXIS 3255	S 3255 L11597	Saccharopolyspora erythraea excisionase (xis) gene, integrase (int) gene.	Sacchampolyenora	
	GB_EST7:W97557	267 W97557	Complete cds's and attB site. mf98a09.r1 Soares mouse embryo NHME13 E 14 E 14.	erythraea	₩-inr-o
rxa02060			IMAGE:422296 5', mRNA sequence.	Mus musculus 42,969	16-Jul-96

-83-	D D	•	(PC	Г/ІВ0	0/00	922
25-Sep-98	27-Aug-99	3-Aug-99	3-Aug-99	1-Jul-98		5-Jan-99	5-Jan-99	24-Jun-98 21-Jul-99
35,724	38,128 36,662	36,662	34,768	99,843		88,679	100,000	38,951 36,774
Homo sapiens Arabidopsis thaliana	Arabidopsis thaliana Homo sapiens	Homo sapiens	Homo sapiens	Corynebacterium e glutamicum		Corynebacterium glutamicum	Corynebacterium	
169045 AC005544 Homo sapiens chromosome 17, clone hRPK.349_A_8, complete sequence. 104738 AL049483 Arabidopsis thaliana DNA chromosome 4, BAC clone F20B18 (ESSA project).	89904 AL049171 Arabidopsis thaliana DNA chromosome 4, BAC clone (ESSA project) 167932 AC008697 Homo sepiens chromosome 5 clone CIT978SKB_70D3, *** SEQUENCING IN	Homo sapie	Homo sapiens chromosome 5 clone CIT978SKB_76P12, *** SEQUENCING IN PROGRESS ***, 54 unordered pieces.	Corynebacterium glutamicum N-acetylglutamylphosphate reductase (argC), Corynebact ornithine acetyltransferase (argJ), N-acetylglutamate kinase (argB), acetylornithine glutamicum transaminase (argB).		Corynebacterium glutamicum ornithine carbamolytransferase (argF) gene, complete cds.		B.subtilis yws[A,B,C] genes and rbs[A,C,D,K,R] genes. fc57a12.y1 Zebrafish WashU MPIMG EST Danio rerio cDNA 5' simitar to TR:Q13151 Q13151 HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A0 ;; mRNA sequence.
169045 AC005544 104738 AL049483	AL049171 2 AC008697	2 AC008697	AC008703	AF049897		Arusisi8 AF041436		292953 AI878071
16904 10473		16793	21397	O n n	3046	516	2 2	593
rx802087 1470 GB_PR3:AC005544 GB_PL1:ATF20818	GB_PL2:ATT25K17 GB_HTG3:AC008697	GB_HTG3:AC008697 167932 AC008697	GB BA2-AEWGG703 213971 AC008703		GB BA2-AE031518	GB_BA2:AF041436		GB_EST36.AI878071
ка02087 1470	rxa02088 1338		xa02159 636				xa02184 504	

xa02205 1002

rxa02305 975

xa02431 899

rxa02446 558

rxa02541 1308

Table 4 (continued)

Al958166

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GB_EST37:A1958166

rxa02200 1233

xa02201 486

xa02202 762

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	(Rel. 52,	Created) 30-Apr-99	14-OCT-1993	(Rel. 52, Created)	23-Apr-92	17-Jun-98	30-Jan-99	16-OCT-1999	16-OCT-1999	24-Jun-97 6-Jul-99	27-Jun-96 27-Aug-99 4-Feb-00	4-Feb-00
. 000	8	37,067	39,409 97.306			72,028	ler 37,958	ler 37,333	er 37,333	39,848 35,830 37,702	37,888 36,420	35.962
Corynebacterium	glutamicum	Sus scrofa	Felis catus Corynebacterium	glutamicum	Mycobacterium avium subsp. paratuberculosis	Mycobacterium tuberculosis	Drosophila melanogaster 37,958	Drosophila melanogaster 37,333	Drosophila melanogaster 37,333	Mycobacterium leprae Rattus norvegicus Rattus norvegicus	Mycobacterium leprae Homo sapiens	Homo sapiens
Table 4 (continued) DNA encoding Dnak protein which is one of heat shock protein from		SSZ82017 Porcine small intestine cDNA library Sus scrofa cDNA clone c12c06 5' Sus scrofa similar to eukaryotic initiation factor 4 gamma, mRNA sequence.	DNA encoding Dnak protein which is one of heat shock protein from	M.paratuberculosis gene for 70 kD heat shock orntain	Mycobacterium tuberculosis H37Rv complete genome; segment 18/162	156362 AC006472 Drosophila melanogaster, chromosome 2B radio Acra, 2010 2010	BACR48G21, complete sequence.		SEQUENCING IN PROGRESS ***, 55 unordered pieces. Mycobacterium leprae cosmid I 822		Homo sapiens chromosome 20 clone RP4-662M14, *** SEQUENCING IN PROGRESS ***, 10 unordered pieces.	Homo sapiens chromosome 20 clone RP4-662M14, *** SEQUENCING IN PROGRESS *** 10 unordered clease
E10832	1,000	202017 L10606	E10832	X59437	35019 Z95324	AC006472	AC010020	AC010020	295398	AF074879 AJ001380 AL023093	AL079336	AL079336
1856	98	308 1887	1856	2179	35019	156362	106541	106541	42498	3316 2641 38916	174772	1/4//2
EM_PAT:E10832	GB EST24.782017		EM_PAT:E10832	GB_BA1:MPHSP70	GB_BA1:MTY13E10	GB_IN2:AC006472	GB_HTG4:AC010020 106541 AC010020	GB_HTG4:AC010020 106541 AC010020	GB_BA1:MLCL622	GB_RO:RNJ001380 GB_BA1:MLCB2548	GB_HTG2:HSJ662M14 174772 AL079336 GB_HTG2:HS1662M14 137772	I WIZO02511:30 11.
rxa02542 777		;	rxa02543 1977			rxa02586 393			rxa02587 2214	rs03217 331		

Exemplification

Example 1: Preparation of total genomic DNA of Corynebacterium glutamicum ATCC 13032

5 A culture of Corynebacterium glutamicum (ATCC 13032) was grown overnight at 30°C with vigorous shaking in BHI medium (Difco). The cells were harvested by centrifugation, the supernatant was discarded and the cells were resuspended in 5 ml buffer-I (5% of the original volume of the culture — all indicated volumes have been calculated for 100 ml of culture volume). Composition of buffer-I: 140.34 g/l sucrose, 2.46 g/l MgSO₄ x 7H₂O, 10 ml/l KH₂PO₄ solution (100 g/l, adjusted to pH 6.7 with 10 KOH), 50 ml/l M12 concentrate (10 g/l (NH₄)₂SO₄, 1 g/l NaCl, 2 g/l MgSO₄ x 7H₂O, 0.2 g/l CaCl₂, 0.5 g/l yeast extract (Difco), 10 ml/l trace-elements-mix (200 mg/l FeSO₄ x H_2O , 10 mg/l $ZnSO_4$ x 7 H_2O , 3 mg/l $MnCl_2$ x 4 H_2O , 30 mg/l H_3BO_3 20 mg/l $CoCl_2$ x 6 H₂O, 1 mg/l NiCl₂ x 6 H₂O, 3 mg/l Na₂MoO₄ x 2 H₂O, 500 mg/l complexing agent (EDTA or critic acid), 100 ml/l vitamins-mix (0.2 mg/l biotin, 0.2 mg/l folic acid, 20 mg/l p-amino benzoic acid, 20 mg/l riboflavin, 40 mg/l ca-panthothenate, 140 mg/l nicotinic acid, 40 mg/l pyridoxole hydrochloride, 200 mg/l myo-inositol). Lysozyme was added to the suspension to a final concentration of 2.5 mg/ml. After an approximately 4 h incubation at 37°C, the cell wall was degraded and the resulting 20 protoplasts are harvested by centrifugation. The pellet was washed once with 5 ml buffer-I and once with 5 ml TE-buffer (10 mM Tris-HCl, 1 mM EDTA, pH 8). The pellet was resuspended in 4 ml TE-buffer and 0.5 ml SDS solution (10%) and 0.5 ml NaCl solution (5 M) are added. After adding of proteinase K to a final concentration of 200 μg/ml, the suspension is incubated for ca.18 h at 37°C. The DNA was purified by extraction with phenol, phenol-chloroform-isoamylalcohol and chloroform-25 isoamylalcohol using standard procedures. Then, the DNA was precipitated by adding 1/50 volume of 3 M sodium acetate and 2 volumes of ethanol, followed by a 30 min incubation at -20°C and a 30 min centrifugation at 12,000 rpm in a high speed centrifuge using a SS34 rotor (Sorvall). The DNA was dissolved in 1 ml TE-buffer containing 20 μg/ml RNaseA and dialysed at 4°C against 1000 ml TE-buffer for at least 3 hours. During this time, the buffer was exchanged 3 times. To aliquots of 0.4 ml of the dialysed DNA solution, 0.4 ml of 2 M LiCl and 0.8 ml of ethanol are added. After a 30

min incubation at -20°C, the DNA was collected by centrifugation (13,000 rpm, Biofuge Fresco, Heraeus, Hanau, Germany). The DNA pellet was dissolved in TE-buffer. DNA prepared by this procedure could be used for all purposes, including southern blotting or construction of genomic libraries.

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Example 2: Construction of genomic libraries in *Escherichia coli* of *Corynebacterium glutamicum* ATCC13032.

Using DNA prepared as described in Example 1, cosmid and plasmid libraries were constructed according to known and well established methods (see e.g., Sambrook, J. et al. (1989) "Molecular Cloning: A Laboratory Manual", Cold Spring Harbor Laboratory Press, or Ausubel, F.M. et al. (1994) "Current Protocols in Molecular Biology", John Wiley & Sons.)

Any plasmid or cosmid could be used. Of particular use were the plasmids pBR322 (Sutcliffe, J.G. (1979) Proc. Natl. Acad. Sci. USA, 75:3737-3741); pACYC177 (Change & Cohen (1978) J. Bacteriol 134:1141-1156), plasmids of the pBS series (pBSSK+, pBSSK- and others; Stratagene, LaJolla, USA), or cosmids as SuperCos1 (Stratagene, LaJolla, USA) or Lorist6 (Gibson, T.J., Rosenthal A. and Waterson, R.H. (1987) Gene 53:283-286. Gene libraries specifically for use in C. glutamicum may be constructed using plasmid pSL109 (Lee, H.-S. and A. J. Sinskey (1994) J. Microbiol. Biotechnol. 4: 256-263).

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Example 3: DNA Sequencing and Computational Functional Analysis

Genomic libraries as described in Example 2 were used for DNA sequencing according to standard methods, in particular by the chain termination method using ABI377 sequencing machines (see e.g., Fleischman, R.D. et al. (1995) "Whole-genome Random Sequencing and Assembly of Haemophilus Influenzae Rd., Science, 269:496-512). Sequencing primers with the following nucleotide sequences were used: 5'-GGAAACAGTATGACCATG-3' or 5'-GTAAAACGACGGCCAGT-3'.

Example 4: In vivo Mutagenesis

In vivo mutagenesis of Corynebacterium glutamicum can be performed by passage of plasmid (or other vector) DNA through E. coli or other microorganisms (e.g. Bacillus spp. or yeasts such as Saccharomyces cerevisiae) which are impaired in their capabilities to maintain

102:93-98).

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the integrity of their genetic information. Typical mutator strains have mutations in the genes for the DNA repair system (e.g., mutHLS, mutD, mutT, etc.; for reference, see Rupp, W.D. (1996) DNA repair mechanisms, in: *Escherichia col*i and *Salmonella*, p. 2277-2294, ASM: Washington.) Such strains are well known to those of ordinary skill in the art. The use of such strains is illustrated, for example, in Greener, A. and Callahan, M. (1994) *Strategies* 7: 32-34.

Example 5: DNA Transfer Between Escherichia coli and Corynebacterium glutamicum

Several Corynebacterium and Brevibacterium species contain endogenous plasmids (as e.g., pHM1519 or pBL1) which replicate autonomously (for review see, e.g., 10 Martin, J.F. et al. (1987) Biotechnology, 5:137-146). Shuttle vectors for Escherichia coli and Corynebacterium glutamicum can be readily constructed by using standard vectors for E. coli (Sambrook, J. et al. (1989), "Molecular Cloning: A Laboratory Manual", Cold Spring Harbor Laboratory Press or Ausubel, F.M. et al. (1994) "Current Protocols in Molecular Biology", John Wiley & Sons) to which a origin or replication for and a 15 suitable marker from Corynebacterium glutamicum is added. Such origins of replication are preferably taken from endogenous plasmids isolated from Corynebacterium and Brevibacterium species. Of particular use as transformation markers for these species are genes for kanamycin resistance (such as those derived from the Tn5 or Tn903 transposons) or chloramphenicol (Winnacker, E.L. (1987) "From Genes to Clones — 20 Introduction to Gene Technology, VCH, Weinheim). There are numerous examples in the literature of the construction of a wide variety of shuttle vectors which replicate in both E. coli and C. glutamicum, and which can be used for several purposes, including gene overexpression (for reference, see e.g., Yoshihama, M. et al. (1985) J. Bacteriol. 162:591-597, Martin J.F. et al. (1987) Biotechnology, 5:137-146 and Eikmanns, B.J. et al. (1991) Gene, 25

Using standard methods, it is possible to clone a gene of interest into one of the shuttle vectors described above and to introduce such a hybrid vector into strains of Corynebacterium glutamicum. Transformation of C. glutamicum can be achieved by protoplast transformation (Kastsumata, R. et al. (1984) J. Bacteriol. 159306-311), electroporation (Liebl, E. et al. (1989) FEMS Microbiol. Letters, 53:399-303) and in cases where special vectors are used, also by conjugation (as described e.g. in Schäfer, A et al.

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(1990) J. Bacterlol. 172:1663-1666). It is also possible to transfer the shuttle vectors for C. glutamicum to E. coli by preparing plasmid DNA from C. glutamicum (using standard methods well-known in the art) and transforming it into E. coli. This transformation step can be performed using standard methods, but it is advantageous to use an Mcr-deficient E. coli strain, such as NM522 (Gough & Murray (1983) J. Mol. Biol. 166:1-19).

Genes may be overexpressed in *C. glutamicum* strains using plasmids which comprise pCG1 (U.S. Patent No. 4,617,267) or fragments thereof, and optionally the gene for kanamycin resistance from TN903 (Grindley, N.D. and Joyce, C.M. (1980) *Proc. Natl. Acad. Sci. USA* 77(12): 7176-7180). In addition, genes may be overexpressed in *C. glutamicum* strains using plasmid pSL109 (Lee, H.-S. and A. J. Sinskey (1994) *J. Microbiol. Biotechnol.* 4: 256-263).

Aside from the use of replicative plasmids, gene overexpression can also be achieved by integration into the genome. Genomic integration in *C. glutamicum* or other Corynebacterium or Brevibacterium species may be accomplished by well-known methods, such as homologous recombination with genomic region(s), restriction endonuclease mediated integration (REMI) (see, e.g., DE Patent 19823834), or through the use of transposons. It is also possible to modulate the activity of a gene of interest by modifying the regulatory regions (e.g., a promoter, a repressor, and/or an enhancer) by sequence modification, insertion, or deletion using site-directed methods (such as homologous recombination) or methods based on random events (such as transposon mutagenesis or REMI). Nucleic acid sequences which function as transcriptional terminators may also be inserted 3' to the coding region of one or more genes of the invention; such terminators are well-known in the art and are described, for example, in Winnacker, E.L. (1987) From Genes to Clones – Introduction to Gene Technology. VCH: Weinheim.

Example 6: Assessment of the Expression of the Mutant Protein

Observations of the activity of a mutated protein in a transformed host cell rely on the fact that the mutant protein is expressed in a similar fashion and in a similar quantity to that of the wild-type protein. A useful method to ascertain the level of transcription of the mutant gene (an indicator of the amount of mRNA available for translation to the gene product) is to perform a Northern blot (for reference see, for example, Ausubel et al.

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(1988) Current Protocols in Molecular Biology, Wiley: New York), in which a primer designed to bind to the gene of interest is labeled with a detectable tag (usually radioactive or chemiluminescent), such that when the total RNA of a culture of the organism is extracted, run on gel, transferred to a stable matrix and incubated with this probe, the binding and quantity of binding of the probe indicates the presence and also the quantity of mRNA for this gene. This information is evidence of the degree of transcription of the mutant gene. Total cellular RNA can be prepared from Corynebacterium glutamicum by several methods, all well-known in the art, such as that described in Bormann, E.R. et al. (1992) Mol. Microbiol. 6: 317-326.

To assess the presence or relative quantity of protein translated from this mRNA, 10 standard techniques, such as a Western blot, may be employed (see, for example, Ausubel et al. (1988) Current Protocols in Molecular Biology, Wiley: New York). In this process, total cellular proteins are extracted, separated by gel electrophoresis, transferred to a matrix such as nitrocellulose, and incubated with a probe, such as an antibody, which specifically binds to the desired protein. This probe is generally tagged with a chemiluminescent or colorimetric label which may be readily detected. The presence and quantity of label observed indicates the presence and quantity of the desired mutant protein present in the cell.

Example 7: Growth of Genetically Modified Corynebacterium glutamicum — Media 20 and Culture Conditions

Genetically modified Corynebacteria are cultured in synthetic or natural growth media. A number of different growth media for Corynebacteria are both well-known and readily available (Lieb et al. (1989) Appl. Microbiol. Biotechnol., 32:205-210; von der Osten et al. (1998) Biotechnology Letters, 11:11-16; Patent DE 4,120,867; Liebl (1992) "The Genus Corynebacterium, in: The Procaryotes, Volume II, Balows, A. et al., eds. Springer-Verlag). These media consist of one or more carbon sources, nitrogen sources, inorganic salts, vitamins and trace elements. Preferred carbon sources are sugars, such as mono-, di-, or polysaccharides. For example, glucose, fructose, mannose, galactose, ribose, sorbose, ribulose, lactose, maltose, sucrose, raffinose, starch or cellulose serve as very good carbon sources. It is also possible to supply sugar to the media via complex compounds such as molasses or other by-products from sugar refinement. It can also be

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advantageous to supply mixtures of different carbon sources. Other possible carbon sources are alcohols and organic acids, such as methanol, ethanol, acetic acid or lactic acid. Nitrogen sources are usually organic or inorganic nitrogen compounds, or materials which contain these compounds. Exemplary nitrogen sources include ammonia gas or ammonia salts, such as NH₄Cl or (NH₄)₂SO₄, NH₄OH, nitrates, urea, amino acids or complex nitrogen sources like corn steep liquor, soy bean flour, soy bean protein, yeast extract, meat extract and others.

Inorganic salt compounds which may be included in the media include the chloride-, phosphorous- or sulfate- salts of calcium, magnesium, sodium, cobalt, molybdenum, potassium, manganese, zinc, copper and iron. Chelating compounds can be added to the medium to keep the metal ions in solution. Particularly useful chelating compounds include dihydroxyphenols, like catechol or protocatechuate, or organic acids, such as citric acid. It is typical for the media to also contain other growth factors, such as vitamins or growth promoters, examples of which include biotin, riboflavin, thiamin, folic acid, nicotinic acid, pantothenate and pyridoxin. Growth factors and salts frequently originate from complex media components such as yeast extract, molasses, corn steep liquor and others. The exact composition of the media compounds depends strongly on the immediate experiment and is individually decided for each specific case. Information about media optimization is available in the textbook "Applied Microbiol. Physiology, A Practical Approach (eds. P.M. Rhodes, P.F. Stanbury, IRL Press (1997) pp. 53-73, ISBN 0 19 963577 3). It is also possible to select growth media from commercial suppliers, like standard 1 (Merck) or BHI (grain heart infusion, DIFCO) or others.

All medium components are sterilized, either by heat (20 minutes at 1.5 bar and 121°C) or by sterile filtration. The components can either be sterilized together or, if necessary, separately. All media components can be present at the beginning of growth, or they can optionally be added continuously or batchwise.

Culture conditions are defined separately for each experiment. The temperature should be in a range between 15°C and 45°C. The temperature can be kept constant or can be altered during the experiment. The pH of the medium should be in the range of 5 to 8.5, preferably around 7.0, and can be maintained by the addition of buffers to the media. An exemplary buffer for this purpose is a potassium phosphate buffer. Synthetic buffers such as MOPS, HEPES, ACES and others can alternatively or simultaneously be used. It

is also possible to maintain a constant culture pH through the addition of NaOH or NH₄OH during growth. If complex medium components such as yeast extract are utilized, the necessity for additional buffers may be reduced, due to the fact that many complex compounds have high buffer capacities. If a fermentor is utilized for culturing the microorganisms, the pH can also be controlled using gaseous ammonia.

The incubation time is usually in a range from several hours to several days. This time is selected in order to permit the maximal amount of product to accumulate in the broth. The disclosed growth experiments can be carried out in a variety of vessels, such as microtiter plates, glass tubes, glass flasks or glass or metal fermentors of different sizes. For screening a large number of clones, the microorganisms should be cultured in microtiter plates, glass tubes or shake flasks, either with or without baffles. Preferably 100 ml shake flasks are used, filled with 10% (by volume) of the required growth medium. The flasks should be shaken on a rotary shaker (amplitude 25 mm) using a speed-range of 100 – 300 rpm. Evaporation losses can be diminished by the maintenance

of a humid atmosphere; alternatively, a mathematical correction for evaporation losses should be performed.

If genetically modified clones are tested, an unmodified control clone or a control clone containing the basic plasmid without any insert should also be tested. The medium is inoculated to an OD₆₀₀ of O.5 – 1.5 using cells grown on agar plates, such as CM plates (10 g/l glucose, 2,5 g/l NaCl, 2 g/l urea, 10 g/l polypeptone, 5 g/l yeast extract, 5 g/l meat extract, 22 g/l NaCl, 2 g/l urea, 10 g/l polypeptone, 5 g/l yeast extract, 5 g/l meat extract, 22 g/l agar, pH 6.8 with 2M NaOH) that had been incubated at 30°C. Inoculation of the media is accomplished by either introduction of a saline suspension of *C. glutamicum* cells from CM plates or addition of a liquid preculture of this bacterium.

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Example 8 - In vitro Analysis of the Function of Mutant Proteins

The determination of activities and kinetic parameters of enzymes is well established in the art. Experiments to determine the activity of any given altered enzyme must be tailored to the specific activity of the wild-type enzyme, which is well within the ability of one of ordinary skill in the art. Overviews about enzymes in general, as well as specific details concerning structure, kinetics, principles, methods, applications and examples for the determination of many enzyme activities may be

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found, for example, in the following references: Dixon, M., and Webb, E.C., (1979) Enzymes. Longmans: London; Fersht, (1985) Enzyme Structure and Mechanism. Freeman: New York; Walsh, (1979) Enzymatic Reaction Mechanisms. Freeman: San Francisco; Price, N.C., Stevens, L. (1982) Fundamentals of Enzymology. Oxford Univ.

Press: Oxford; Boyer, P.D., ed. (1983) The Enzymes, 3rd ed. Academic Press: New York; Bisswanger, H., (1994) Enzymkinetik, 2nd ed. VCH: Weinheim (ISBN 3527300325); Bergmeyer, H.U., Bergmeyer, J., Graßl, M., eds. (1983-1986) Methods of Enzymatic Analysis, 3rd ed., vol. I-XII, Verlag Chemie: Weinheim; and Ullmann's Encyclopedia of Industrial Chemistry (1987) vol. A9, "Enzymes". VCH: Weinheim, p. 352-363.

The activity of proteins which bind to DNA can be measured by several well-established methods, such as DNA band-shift assays (also called gel retardation assays). The effect of such proteins on the expression of other molecules can be measured using reporter gene assays (such as that described in Kolmar, H. et al. (1995) EMBO J. 14: 3895-3904 and references cited therein). Reporter gene test systems are well known and established for applications in both pro- and eukaryotic cells, using enzymes such as beta-galactosidase, green fluorescent protein, and several others.

The determination of activity of membrane-transport proteins can be performed according to techniques such as those described in Gennis, R.B. (1989) "Pores, Channels and Transporters", in Biomembranes, Molecular Structure and Function, Springer: Heidelberg, p. 85-137; 199-234; and 270-322.

Example 9: Analysis of Impact of Mutant Protein on the Production of the Desired Product

The effect of the genetic modification in *C. glutamicum* on production of a desired compound (such as an amino acid) can be assessed by growing the modified microorganism under suitable conditions (such as those described above) and analyzing the medium and/or the cellular component for increased production of the desired product (*i.e.*, an amino acid). Such analysis techniques are well known to one of ordinary skill in the art, and include spectroscopy, thin layer chromatography, staining methods of various kinds, enzymatic and microbiological methods, and analytical chromatography such as high performance liquid chromatography (see, for example,

Ullman, Encyclopedia of Industrial Chemistry, vol. A2, p. 89-90 and p. 443-613, VCH: Weinheim (1985); Fallon, A. et al., (1987) "Applications of HPLC in Biochemistry" in: Laboratory Techniques in Biochemistry and Molecular Biology, vol. 17; Rehm et al. (1993) Biotechnology, vol. 3, Chapter III: "Product recovery and purification", page 469-714, VCH: Weinheim; Belter, P.A. et al. (1988) Bioseparations: downstream processing for biotechnology, John Wiley and Sons; Kennedy, J.F. and Cabral, J.M.S. (1992) Recovery processes for biological materials, John Wiley and Sons; Shaeiwitz, J.A. and Henry, J.D. (1988) Biochemical separations, in: Ulmann's Encyclopedia of Industrial Chemistry, vol. B3, Chapter 11, page 1-27, VCH: Weinheim; and Dechow,
F.J. (1989) Separation and purification techniques in biotechnology, Noyes Publications.)

In addition to the measurement of the final product of fermentation, it is also possible to analyze other components of the metabolic pathways utilized for the production of the desired compound, such as intermediates and side-products, to

15 determine the overall yield, production, and/or efficiency of production of the compound. Analysis methods include measurements of nutrient levels in the medium (e.g., sugars, hydrocarbons, nitrogen sources, phosphate, and other ions), measurements of biomass composition and growth, analysis of the production of common metabolites of biosynthetic pathways, and measurement of gasses produced during fermentation.

20 Standard methods for these measurements are outlined in Applied Microbial Physiology, A Practical Approach, P.M. Rhodes and P.F. Stanbury, eds., IRL Press, p. 103-129; 131-163; and 165-192 (ISBN: 0199635773) and references cited therein.

Example 10: Purification of the Desired Product from C. glutamicum Culture

Recovery of the desired product from the *C. glutamicum* cells or supernatant of the above-described culture can be performed by various methods well known in the art. If the desired product is not secreted from the cells, the cells can be harvested from the culture by low-speed centrifugation, the cells can be lysed by standard techniques, such as mechanical force or sonication. The cellular debris is removed by centrifugation, and the supernatant fraction containing the soluble proteins is retained for further purification of the desired compound. If the product is secreted from the *C. glutamicum*

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cells, then the cells are removed from the culture by low-speed centrifugation, and the supernate fraction is retained for further purification.

The supernatant fraction from either purification method is subjected to chromatography with a suitable resin, in which the desired molecule is either retained on a chromatography resin while many of the impurities in the sample are not, or where the impurities are retained by the resin while the sample is not. Such chromatography steps may be repeated as necessary, using the same or different chromatography resins. One of ordinary skill in the art would be well-versed in the selection of appropriate chromatography resins and in their most efficacious application for a particular molecule to be purified. The purified product may be concentrated by filtration or ultrafiltration, and stored at a temperature at which the stability of the product is maximized.

There are a wide array of purification methods known to the art and the preceding method of purification is not meant to be limiting. Such purification techniques are described, for example, in Bailey, J.E. & Ollis, D.F. Biochemical Engineering Fundamentals, McGraw-Hill: New York (1986).

The identity and purity of the isolated compounds may be assessed by techniques standard in the art. These include high-performance liquid chromatography (HPLC), spectroscopic methods, staining methods, thin layer chromatography, NIRS, enzymatic assay, or microbiologically. Such analysis methods are reviewed in: Patek et al. (1994)

20 Appl. Environ. Microbiol. 60: 133-140; Malakhova et al. (1996) Biotekhnologiya 11: 27-32; and Schmidt et al. (1998) Bioprocess Engineer. 19: 67-70. Ulmann's Encyclopedia of Industrial Chemistry, (1996) vol. A27, VCH: Weinheim, p. 89-90, p. 521-540, p. 540-547, p. 559-566, 575-581 and p. 581-587; Michal, G. (1999) Biochemical Pathways: An Atlas of Biochemistry and Molecular Biology, John Wiley and Sons; Fallon, A. et al. (1987) Applications of HPLC in Biochemistry in: Laboratory Techniques in Biochemistry and Molecular Biology, vol. 17.

EXAMPLE 11: Cloning of a *Corynebacterium glutamicum* Gene Involved in Lincomycin Resistance Using a Reporter Gene Approach

A. Identification of the Gene Encoding the LMRB Protein

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Plasmid pSL130 was constructed by ligation of the aceB promoter region (paceB) of C. glutamicum (Kim, H.J. et al. (1997) J. Microbiol. Biotechnol. 7: 287-292) into the polylinker of the lac operon fusion vector pRS415, which lacks a promoter (Simon, R.W. et al. (1987) Gene 53: 85-96). Plasmid pSL145 was constructed by ligating the resulting paceB-lac region into the E. coli cloning vector pACYC184. E. coli DH5aF' was transformed with pSL145 and the resulting strain was used as a host for screening of a genomic C. glutamicum library (in pSL109).

Transformants were screened by growth on agar medium containing 5-bromo-4-chloro-3-indolyl-beta-D-glalactopyranoside (X-Gal). A white colony, containing DNA influencing lacZ expression, was selected for further analysis. This clone was found to contain a 4 kB fragment from the gene library. Subclones were constructed in pSL109 and a subclone which retained the white phenotype on X-Gal plates was identified. This subclone was found to contain a 2.6 kB BamH1-XhoI fragment (plasmid pSL149-5). The fragment was sequenced and identified as a membrane protein-encoding gene (LMRB gene).

The 1442 nucleotides of the coding sequence of the LMRB gene encode a polypeptide of 481 amino acid residues with a high percentage of hydrophobic amino acids. A Genbank search determined that the LMRB protein is 40% identical to the protein product of the lmrB gene from *Bacillus subtilis* (Genbank Accession AL009126, TREMBL Accession P94422), as determined using a CLUSTAL W analysis (using standard parameters).

The LMRN protein contains a sequence pattern: 158-A-P-A-L-G-P-T-L-S-G-167 (SEQ ID NO:301), which resembles the known multi-drug-resistance-protein consensus motif G-X-X-X-G-P-X-X-G-G (SEQ ID NO:302) (Paulsen, I.T., and Skurray, R.A. (1993) *Gene* 124: 1-11). Therefore, the LMRB protein was classified as a drug resistance protein.

B. In vivo Analysis of lmrB Function

The lmrB gene was overexpressed in *C. glutamicum* ASO19E12 (Kim, H.J. et al. 30 (1997) *J. Microbiol. Biotechnol.* 7: 287-292) using the plasmid pSL149-5, described above.

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- Disruption of the LMRB gene was accomplished by use of the vector pSL18-lmrB. This vector was constructed as follows: an internal fragment of the LMRB gene was amplified by PCR under standard conditions using primers 5'-CTCCAGGATTGCTCCGAAGG-3' (SEQ ID NO:303) and 5'-
- 5 CACAGTGGTTGACCACTGGC-3' (SEQ ID NO:304). The resulting PCR product was treated with T7 DNA polymerase and T7 polynucleotide kinase, and was cloned into the Smal site of plasmid pSL18 (Kim, Y.H. and H.-S. Lee (1996) J. Microbiol. Biotechnol. 6: 315-320). The disruption of the LMRB gene in C. glutamicum ASO19E12 was performed by conjugation, as previously described (Schwarzer and Puhler (1991) Bio/Technology 9:84-87).

C. glutamicum cells transformed with pSL149-5 displayed similar resistances as untransformed cells against erythromycin, penicillin G, tetracycline, chloramphenicol, spectinomycin, nalidixic acid, gentamycin, streptomycin, ethidium bromide, carbonyl cyanide m-chlorophenylhydrazone (CCCP), and sodium dodecyl sulfate. Significant differences were observed, however, in the resistance of transformed and untransformed cells to lincomycin.

LMRB-overexpressing C. glutamicum cells were found to be able to grow in the presence of 20 µg/ml lincomycin. In contrast, cells which do not overexpress LMRB (or cells carrying a LMRB disruption) were not able to grow on agar media containing 5 µg/ml lincomycin. This effect was clearly visible in liquid culture. LMRB overexpression led to a 9-fold increased resistance (compared to wild-type) against lincomycin and LMRB disruption resulted in a decreased resistance (28% of wild-type) to this antibiotic.

25 Example 12: Analysis of the Gene Sequences of the Invention

The comparison of sequences and determination of percent homology between two sequences are art-known techniques, and can be accomplished using a mathematical algorithm, such as the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci.* USA 87:2264-68, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci.* USA 90:5873-77. Such an algorithm is incorporated into the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100,

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wordlength = 12 to obtain nucleotide sequences homologous to SRT nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to SRT protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., (1997) Nucleic Acids Res. 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, one of ordinary skill in the art will know how to optimize the parameters of the program (e.g., XBLAST and NBLAST) for the specific sequence being analyzed.

Another example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Meyers and Miller ((1988) Comput. Appl. Biosci. 4: 11-17). Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Additional algorithms for sequence analysis are known in the art, and include ADVANCE and ADAM. described in Torelli and Robotti (1994) Comput. Appl. Biosci. 10:3-5; and FASTA, described in Pearson and Lipman (1988) P.N.A.S. 85:2444-8.

The percent homology between two amino acid sequences can also be accomplished using the GAP program in the GCG software package (available at http://www.gcg.com), using either a Blosum 62 matrix or a PAM250 matrix, and a gap weight of 12, 10, 8, 6, or 4 and a length weight of 2, 3, or 4. The percent homology between two nucleic acid sequences can be accomplished using the GAP program in the GCG software package, using standard parameters, such as a gap weight of 50 and a length weight of 3.

A comparative analysis of the gene sequences of the invention with those present in Genbank has been performed using techniques known in the art (see, e.g., Bexevanis and Ouellette, eds. (1998) Bioinformatics: A Practical Guide to the Analysis of Genes and Proteins. John Wiley and Sons: New York). The gene sequences of the invention were compared to genes present in Genbank in a three-step process. In a first step, a BLASTN analysis (e.g., a local alignment analysis) was performed for each of the sequences of the invention against the nucleotide sequences present in Genbank, and the

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top 500 hits were retained for further analysis. A subsequent FASTA search (e.g., a combined local and global alignment analysis, in which limited regions of the sequences are aligned) was performed on these 500 hits. Each gene sequence of the invention was subsequently globally aligned to each of the top three FASTA hits, using the GAP program in the GCG software package (using standard parameters). In order to obtain correct results, the length of the sequences extracted from Genbank were adjusted to the length of the query sequences by methods well-known in the art. The results of this analysis are set forth in Table 4. The resulting data is identical to that which would have been obtained had a GAP (global) analysis alone been performed on each of the genes of the invention in comparison with each of the references in Genbank, but required significantly reduced computational time as compared to such a database-wide GAP (global) analysis. Sequences of the invention for which no alignments above the cutoff values were obtained are indicated on Table 4 by the absence of alignment information. It will further be understood by one of ordinary skill in the art that the GAP alignment homology percentages set forth in Table 4 under the heading "% homology (GAP)" are listed in the European numerical format, wherein a ',' represents a decimal point. For example, a value of "40,345" in this column represents "40.345%".

Example 13: Construction and Operation of DNA Microarrays

The sequences of the invention may additionally be used in the construction and application of DNA microarrays (the design, methodology, and uses of DNA arrays are well known in the art, and are described, for example, in Schena, M. et al. (1995)

Science 270: 467-470; Wodicka, L. et al. (1997) Nature Biotechnology 15: 1359-1367;

DeSaizieu, A. et al. (1998) Nature Biotechnology 16: 45-48; and DeRisi, J.L. et al.

(1997) Science 278: 680-686).

DNA microarrays are solid or flexible supports consisting of nitrocellulose, nylon, glass, silicone, or other materials. Nucleic acid molecules may be attached to the surface in an ordered manner. After appropriate labeling, other nucleic acids or nucleic acid mixtures can be hybridized to the immobilized nucleic acid molecules, and the label may be used to monitor and measure the individual signal intensities of the hybridized molecules at defined regions. This methodology allows the simultaneous quantification of the relative or absolute amount of all or selected nucleic acids in the applied nucleic

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acid sample or mixture. DNA microarrays, therefore, permit an analysis of the expression of multiple (as many as 6800 or more) nucleic acids in parallel (see, e.g., Schena, M. (1996) *BioEssays* 18(5): 427-431).

The sequences of the invention may be used to design oligonucleotide primers which are able to amplify defined regions of one or more *C. glutamicum* genes by a nucleic acid amplification reaction such as the polymerase chain reaction. The choice and design of the 5' or 3' oligonucleotide primers or of appropriate linkers allows the covalent attachment of the resulting PCR products to the surface of a support medium described above (and also described, for example, Schena, M. *et al.* (1995) *Science* 270: 467-470).

Nucleic acid microarrays may also be constructed by in situ oligonucleotide synthesis as described by Wodicka, L. et al. (1997) Nature Biotechnology 15: 1359-1367. By photolithographic methods, precisely defined regions of the matrix are exposed to light. Protective groups which are photolabile are thereby activated and undergo nucleotide addition, whereas regions that are masked from light do not undergo any modification. Subsequent cycles of protection and light activation permit the synthesis of different oligonucleotides at defined positions. Small, defined regions of the genes of the invention may be synthesized on microarrays by solid phase oligonucleotide synthesis.

The nucleic acid molecules of the invention present in a sample or mixture of nucleotides may be hybridized to the microarrays. These nucleic acid molecules can be labeled according to standard methods. In brief, nucleic acid molecules (e.g., mRNA molecules or DNA molecules) are labeled by the incorporation of isotopically or fluorescently labeled nucleotides, e.g., during reverse transcription or DNA synthesis.

Hybridization of labeled nucleic acids to microarrays is described (e.g., in Schena, M. et al. (1995) supra; Wodicka, L. et al. (1997), supra; and DeSaizieu A. et al. (1998), supra). The detection and quantification of the hybridized molecule are tailored to the specific incorporated label. Radioactive labels can be detected, for example, as described in Schena, M. et al. (1995) supra) and fluorescent labels may be detected, for example, by the method of Shalon et al. (1996) Genome Research 6: 639-645).

The application of the sequences of the invention to DNA microarray technology, as described above, permits comparative analyses of different strains of C.

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glutamicum or other Corynebacteria. For example, studies of inter-strain variations based on individual transcript profiles and the identification of genes that are important for specific and/or desired strain properties such as pathogenicity, productivity and stress tolerance are facilitated by nucleic acid array methodologies. Also, comparisons of the profile of expression of genes of the invention during the course of a fermentation reaction are possible using nucleic acid array technology.

Example 14: Analysis of the Dynamics of Cellular Protein Populations (Proteomics)

The genes, compositions, and methods of the invention may be applied to study the interactions and dynamics of populations of proteins, termed 'proteomics'. Protein populations of interest include, but are not limited to, the total protein population of C. glutamicum (e.g., in comparison with the protein populations of other organisms), those proteins which are active under specific environmental or metabolic conditions (e.g., during fermentation, at high or low temperature, or at high or low pH), or those proteins which are active during specific phases of growth and development.

Protein populations can be analyzed by various well-known techniques, such as gel electrophoresis. Cellular proteins may be obtained, for example, by lysis or extraction, and may be separated from one another using a variety of electrophoretic techniques. Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) separates proteins largely on the basis of their molecular weight. Isoelectric focusing polyacrylamide gel electrophoresis (IEF-PAGE) separates proteins by their isoelectric point (which reflects not only the amino acid sequence but also posttranslational modifications of the protein). Another, more preferred method of protein analysis is the consecutive combination of both IEF-PAGE and SDS-PAGE, known as 2-D-gel electrophoresis (described, for example, in Hermann et al. (1998) Electrophoresis 19: 3217-3221; Fountoulakis et al. (1998) Electrophoresis 19: 1193-1202; Langen et al. (1997) Electrophoresis 18: 1184-1192; Antelmann et al. (1997) Electrophoresis 18: 1451-1463). Other separation techniques may also be utilized for protein separation, such as capillary gel electrophoresis; such techniques are well known in the art.

Proteins separated by these methodologies can be visualized by standard techniques, such as by staining or labeling. Suitable stains are known in the art, and

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include Coomassie Brilliant Blue, silver stain, or fluorescent dyes such as Sypro Ruby (Molecular Probes). The inclusion of radioactively labeled amino acids or other protein precursors (e.g., ³⁵S-methionine, ³⁵S-cysteine, ¹⁴C-labelled amino acids, ¹⁵N-amino acids, ¹⁵NO₃ or ¹⁵NH₄⁺ or ¹³C-labelled amino acids) in the medium of *C. glutamicum* permits the labeling of proteins from these cells prior to their separation. Similarly, fluorescent labels may be employed. These labeled proteins can be extracted, isolated and separated according to the previously described techniques.

Proteins visualized by these techniques can be further analyzed by measuring the amount of dye or label used. The amount of a given protein can be determined quantitatively using, for example, optical methods and can be compared to the amount of other proteins in the same gel or in other gels. Comparisons of proteins on gels can be made, for example, by optical comparison, by spectroscopy, by image scanning and analysis of gels, or through the use of photographic films and screens. Such techniques are well-known in the art.

To determine the identity of any given protein, direct sequencing or other standard techniques may be employed. For example, N- and/or C-terminal amino acid sequencing (such as Edman degradation) may be used, as may mass spectrometry (in particular MALDI or ESI techniques (see, e.g., Langen et al. (1997) Electrophoresis 18: 1184-1192)). The protein sequences provided herein can be used for the identification of C. glutamicum proteins by these techniques.

The information obtained by these methods can be used to compare patterns of protein presence, activity, or modification between different samples from various biological conditions (e.g., different organisms, time points of fermentation, media conditions, or different biotopes, among others). Data obtained from such experiments alone, or in combination with other techniques, can be used for various applications, such as to compare the behavior of various organisms in a given (e.g., metabolic) situation, to increase the productivity of strains which produce fine chemicals or to increase the efficiency of the production of fine chemicals.

Equivalents ·

Those of ordinary skill in the art will recognize, or will be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed:

- 1. An isolated nucleic acid molecule from Corynebacterium glutamicum encoding a stress, resistance, or tolerance gene, or a portion thereof, provided that the nucleic acid molecule does not consist of any of the F-designated genes set forth in Table 1.
- The isolated nucleic acid molecule of claim 1, wherein said stress, resistance, or tolerance gene is selected from the group consisting of nucleic acid molecules involved in a stress response, tolerance, or resistance to temperature stresses, pH stresses, oxygen stresses, osmotic stresses, toxic chemicals, oxygen radicals, antibiotics, or to lincomycin.
- 3. An isolated Corynebacterium glutamicum nucleic acid molecule selected from the group consisting of those sequences set forth as odd-numbered SEQ ID NOs of the Sequence Listing, or a portion thereof, provided that the nucleic acid molecule does not consist of any of the F-designated genes set forth in Table 1.
- 4. An isolated nucleic acid molecule which encodes a polypeptide sequence selected from the group consisting of those sequences set forth as even-numbered SEQ ID NOs of the Sequence Listing, provided that the nucleic acid molecule does not consist of any of the F-designated genes set forth in Table 1.
- 5. An isolated nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide selected from the group of amino acid sequences consisting of those sequences set forth as even-numbered SEQ ID NOs of the Sequence Listing, provided that the nucleic acid molecule does not consist of any of the F-designated genes set forth in Table 1.
- 30 6. An isolated nucleic acid molecule comprising a nucleotide sequence which is at least 50% homologous to a nucleotide sequence selected from the group consisting of those sequences set forth as odd-numbered SEQ ID NOs of the Sequence Listing, or

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a portion thereof, provided that the nucleic acid molecule does not consist of any of the F-designated genes set forth in Table 1.

- 7. An isolated nucleic acid molecule comprising a fragment of at least 15 nucleotides of a nucleic acid comprising a nucleotide sequence selected from the group consisting of those sequences set forth as odd-numbered SEQ ID NOs of the Sequence Listing, provided that the nucleic acid molecule does not consist of any of the F-designated genes set forth in Table 1.
- 10 8. An isolated nucleic acid molecule which hybridizes to the nucleic acid molecule of any one of claims 1-7 under stringent conditions.
 - An isolated nucleic acid molecule comprising the nucleic acid molecule of any one
 of claims 1-8 or a portion thereof and a nucleotide sequence encoding a heterologous
 polypeptide.
 - 10. A vector comprising the nucleic acid molecule of any one of claims 1-9.
 - 11. The vector of claim 10, which is an expression vector.
 - 12. A host cell transfected with the expression vector of claim 11.
 - 13. The host cell of claim 12, wherein said cell is a microorganism.
- 25 14. The host cell of claim 13, wherein said cell belongs to the genus Corynebacterium or Brevibacterium.
 - 15. The host cell of claim 12, wherein the expression of said nucleic acid molecule results in the modulation in production of a fine chemical from said cell.
 - 16. The host cell of claim 15, wherein said fine chemical is selected from the group consisting of: organic acids, proteinogenic and nonproteinogenic amino acids, purine

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and pyrimidine bases, nucleosides, nucleotides, lipids, saturated and unsaturated fatty acids, diols, carbohydrates, aromatic compounds, vitamins, cofactors, polyketides, and enzymes.

- 5 17. A method of producing a polypeptide comprising culturing the host cell of claim 12 in an appropriate culture medium to, thereby, produce the polypeptide.
 - 18. An isolated stress, resistance, or tolerance polypeptide from *Corynebacterium* glutamicum, or a portion thereof.
 - 19. The protein of claim 18, wherein said stress, resistance, or tolerance polypeptide is selected from the group consisting of proteins involved in a stress response, tolerance, or resistance to temperature stresses, pH stresses, oxygen stresses, osmotic stresses, toxic chemicals, oxygen radicals, antibiotics, or to lincomycin.
 - 20. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of those sequences set forth as even-numbered SEQ ID NOs of the Sequence Listing, provided that the amino acid sequence is not encoded by any of the F-designated genes set forth in Table 1.
 - 21. An isolated polypeptide comprising a naturally occurring allelic variant of a polypeptide comprising an amino acid sequence selected from the group consisting of those sequences set forth as even-numbered SEQ ID NOs of the Sequence Listing, or a portion thereof, provided that the amino acid sequence is not encoded by any of the F-designated genes set forth in Table 1.
 - 22. The isolated polypeptide of any of claims 18-21, further comprising heterologous amino acid sequences.
- 30 23. An isolated polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 50% homologous to a nucleic acid selected from the group consisting of those sequences set forth as odd-numbered SEQ ID

NOs of the Sequence Listing,, provided that the nucleic acid molecule does not consist of any of the F-designated nucleic acid molecules set forth in Table 1.

- 24. An isolated polypeptide comprising an amino acid sequence which is at least 50% homologous to an amino acid sequence selected from the group consisting of those sequences set forth as even-numbered SEQ ID NOs of the Sequence Listing, provided that the amino acid sequence is not encoded by any of the F-designated genes set forth in Table 1.
- 25. A method for producing a fine chemical, comprising culturing a cell containing a vector of claim 12 such that the fine chemical is produced.
 - 26. The method of claim 25, wherein said method further comprises the step of recovering the fine chemical from said culture.
 - 27. The method of claim 25, wherein said method further comprises the step of transfecting said cell with the vector of claim 11 to result in a cell containing said vector.
- 28. The method of claim 25, wherein said cell belongs to the genus Corynebacterium or Brevibacterium.
 - 29. The method of claim 25, wherein said cell is selected from the group consisting of: Corynebacterium glutamicum, Corynebacterium herculis, Corynebacterium, lilium,
- 25 Corynebacterium acetoacidophilum, Corynebacterium acetoglutamicum,
 Corynebacterium acetophilum, Corynebacterium ammoniagenes, Corynebacterium
 fujiokense, Corynebacterium nitrilophilus, Brevibacterium ammoniagenes,
 Brevibacterium butanicum, Brevibacterium divaricatum, Brevibacterium flavum,
 Brevibacterium healii, Brevibacterium ketoglutamicum, Brevibacterium
- 30 ketosoreductum, Brevibacterium lactofermentum, Brevibacterium linens, Brevibacterium paraffinolyticum, and those strains set forth in Table 3.

- 30. The method of claim 25, wherein expression of the nucleic acid molecule from said vector results in modulation of production of said fine chemical.
- 31. The method of claim 25, wherein said fine chemical is selected from the group consisting of: organic acids, proteinogenic and nonproteinogenic amino acids, purine and pyrimidine bases, nucleosides, nucleotides, lipids, saturated and unsaturated fatty acids, diols, carbohydrates, aromatic compounds, vitamins, cofactors, polyketides and enzymes.
- 10 32. The method of claim 25, wherein said fine chemical is an amino acid.
 - 33. The method of claim 32, wherein said amino acid is drawn from the group consisting of: lysine, glutamate, glutamine, alanine, aspartate, glycine, serine, threonine, methionine, cysteine, valine, leucine, isoleucine, arginine, proline, histidine, tyrosine, phenylalanine, and tryptophan.
 - 34. A method for producing a fine chemical, comprising culturing a cell whose genomic DNA has been altered by the inclusion of a nucleic acid molecule of any one of claims 1-9.

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- 35. A method for diagnosing the presence or activity of Corynebacterium diphtheriae in a subject, comprising detecting the presence of one or more SEQ ID NOs 1 through 304 of the Sequence Listing in the subject, provided that the sequences are not or are not encoded by any of the F-designated sequences set forth in Table 1, thereby diagnosing the presence or activity of Corynebacterium diphtheriae in the subject.
- 36. A host cell comprising a nucleic acid molecule selected from the group consisting of the nucleic acid molecules set forth as odd-numbered SEQ ID NOs of the Sequence Listing, wherein the nucleic acid molecule is disrupted.

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37. A host cell comprising a nucleic acid molecule selected from the group consisting of the nucleic acid molecules set forth as odd-numbered SEQ ID NOs of the

- Sequence Listing, wherein the nucleic acid molecule comprises one or more nucleic acid modifications from the sequence set forth as odd-numbered SEQ ID NOs of the Sequence Listing.
- 38. A host cell comprising a nucleic acid molecule selected from the group consisting of the nucleic acid molecules set as odd-numbered SEQ ID NOs of the Sequence Listing, wherein the regulatory region of the nucleic acid molecule is modified relative to the wild-type regulatory region of the molecule.

SEQUENCE LISTING

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ga G1	a ac	c at	t ct	g tc	gtt	gco	tte	cct	tc	ato	ato	gaa	gat	tto	tcc	259
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ato	gtt	cag	gcq	gtt	ggt	act	aca	cta	ata	ato	cct	++~	ot-	- - -		400
Ile	Val	Gln	Ala	Val	Gly	Thr	Ala	Leu	Val	Met	Pro	Leu	Leu	acg Met	acg Thr	499

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Gly Phe M 65	et Leu Thr	Met Ala Va 70	l Val Ile	Pro Thr Th	r Gly Tyr Le 8	eu 80



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- Leu Leu Gly Ala Arg Ile Val Gln Ala Val Gly Thr Ala Leu Val Met 115 120 125
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- Trp Leu Phe Trp Met Met Leu Pro Ile Val Val Ile Ala Leu Val Ile 180 185 190
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- Arg Ala Phe Lys Val Arg Asn Phe Ser Phe Ser Leu Thr Thr Ile Leu 275 280 285
- Leu Ala Phe Gly Ala Met Leu Gly Thr Val Met Val Leu Pro Ile Tyr 290 295 300
- Leu Gln Thr Ser Leu Gly Val Thr Ala Leu Val Thr Gly Leu Val Val 305 310 315 320
- Met Pro Gly Gly Leu Leu Gln Gly Leu Ile Ser Pro Phe Ile Gly Arg 325 330 335
- Phe Tyr Asp Lys Val Gly Pro Arg Pro Leu Leu Ile Pro Gly Ala Ile 340 345 350
- Ala Leu Ala Ile Ala Ala Ser Ser Met Thr Phe Leu Asn Glu Asn Ser 355 360 365
- Pro Val Trp Met Val Val Met His Val Val Phe Ser Ile Gly Met 370 375 380

38		 				90 10 Fe	eu me	et T	nr T		95	.eu	GIŸ	ATa	Let	400	
. Lý	ş Hi	s Le	eu Ty		ly H: 05	s Gl	.y S€	er A		le Ł 10	eu A	lsn	Thr	Phe	Glr 415	n Gln	
Le	u Al	.a G]	ly Al 42		la Gl	y Th	r Al	la II 42		et I	le A	la	Ala	Leu 430		Phe	
Gl	y Th	r Se 43		.e Al	la Al	a Se	r Se 44		ly Se	er A	la H		Ala 445	Glu	Ala	Val	
Al	a Al 45		y Th	r Ly	s Va	1 Al 45		e Il	.e Al	la G		la 60	Ile	Ile	Ala	Val	
I1 46	e Al 5	a Le	u Va	l Va	1 Se 47		u Ph	e Va	1 Th	1r A1		al (Glu	Glu	Glu	Ala 480	
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aac Asn	gtc Val	aac Asn 5	Ile	aag Lys	ccg Pro	ctt Leu	gag Glu 10	Asp	aaq Lys	g ato	c ct e Le	u V	tt (al (15	cag Gln	atc Ile	aac Asn	105
gaa Glu	gca Ala 20	gag Glu	acc Thr	acc Thr	acc Thr	gct Ala 25	tcc Ser	ggc	Lev	gto Val	at l Il	e P	ca q ro A	yat Asp	tcc Ser	gct Ala	153
aag Lys 35	gaa Glu	aag Lys	cca Pro	ca a Gln	gag Glu 40	gca Ala	acc Thr	gtt Val	ato	gca Ala 45	Va.	t gg	ge c	ro (ggc Gly	cgc Arg 50	201
ttc Phe	gat Asp	gac Asp	aag Lys	ggt Gly 55	aac Asn	cgc Arg	atc Ile	cca Pro	ctg Leu 60	gac Asp	ato Ile	c aa e Ly	ag g /s G	aa d lu l	gat Asp 65	gac Asp	249
gtt Val	gtg Val	atc Įle	ttc Phe 70	tcc Ser	cgt Arg	tac Tyr	ggc Gly	ggc Gly 75	acc Thr	gag Glu	ato Ile	aa Ly	s P	tc d he 0 80	ggt Ely	ggc Gly	297

gtg gag tac ttg ctt ctc tcc gct cgt gac atc ctc gca atc gtc gag Val Glu Tyr Leu Leu Ser Ala Arg Asp Ile Leu Ala Ile Val Glu 85 90 95

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Gly Arg Phe Asp Asp Lys Gly Asn Arg Ile Pro Leu Asp Ile Lys Glu
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Asp Asp Val Val Ile Phe Ser Arg Tyr Gly Gly Thr Glu Ile Lys Phe 65 70 75 80

Gly Gly Val Glu Tyr Leu Leu Leu Ser Ala Arg Asp Ile Leu Ala Ile 85 90 95

Val Glu Lys

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Met Ala Lys Leu Ile

1 5

gct ttt gac cag gac gcc cgc gaa ggc att ctc cgg ggc gtt gac gct 163 Ala Phe Asp Gln Asp Ala Arg Glu Gly Ile Leu Arg Gly Val Asp Ala 10 15 20

				25	· ·	Lys	vai	Inr	30	Gly	Pro	cgc Arg	Gly	Arg 1 35	Asn '	Val	211
	var	Deu	40	nys	ura 1	ene (этА	45	Pro	Leu	Val	acc Thr	Asn 7	Asp (Sly V	/al	259
	acc Thr	att Ile 55	gcc Ala	cgc Arg /	gac a Asp 1	itc d le A	sp 60	ctt Leu	gag Glu	gat Asp	cct Pro	ttt (Phe (65	gag a Slu A	aac d Asn I	tc g eu G	gt Sly	307
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	gac Asp	ggc Gly	acc a Thr 1	acg a Thr T	ct g hr A 90	ca a la T	ct c	etg (Leu)	ctt Leu i	gct (Ala (95	cag (Gln <i>l</i>	gca c Ala L	tc a eu I	le A	ct g la G 00	aa lu	403
	ggc Gly	ctg (Leu <i>l</i>	9	ac g sn V 05	tt go al Al	et go	ct g la G	TA	gca a Ala ≇ L10	aac d Asn I	cca a Pro M	itg g let G	lu L	tc aa eu As 15	ac aa an Ly	ag ys	451
	ggt a	1	20	- G A.	ra Ai	a Gi	1.	ys 1 25	nr L	eu G	ilu G	lu Le 13	eu Ly 30	ys Al	a Ar	g	499
	gca a Ala I 1	hcc g hr G .35	ag gʻ lu Va	tg to al Se	et ga er As	c ac p Th 14	r 17	ag g ys G	aa a lu I	tc g le A	la A	ac gt sn Va 45	c go l Al	t ac .a Th	c gt r Va	t	547
	tca t Ser S 150	er A	gc ga rg As	it ga sp Gl	a gt u Vai 15	· va.	c go l Gl	jc ga .y G	ag a lu I	re v	tt go al Al 60	et ge la Al	a go a Al	g at a Me	g ga t Gl 16	u	595
;	aag g Lys V	tt gg al Gi	gc aa Ly Ly	g ga 's As _i 17	5 977	gto Val	gt Va	c ac l Th	ec gt ar Va 17	IT G1	ag ga lu Gl	g tc u Se	c ca r Gl:	g tco n Sei 180	: Įl	C B	643
Ċ	gag ad Glu Th	et go er Al	t ct a Le	a ore	g gtc 1 Val	acc	ga.	a gg u Gl 19	A II	t to e Se	t tt r Ph	c gad e Asp	Lys	s Gly	tac Tyr	2	691
L	tt to eu Se	er Pr 20	~ - 7 -	t tto Phe	atc Ile	aac Asn	gad Asp 205	AS	c ga n As	c ac p Th	t cad	g cag n Gln 210	. Ala	gtc Val	ctg Leu	ſ	739
g A	ac aa sp As 21		t gca o Ala	gtg Val	ctg Leu	ctt Leu 220	gtt Val	cgo Arg	c aad g Ası	c aaq	g att s Ile 225	e Ser	tcc Ser	ctc Leu	cca Pro		787
	ac tto sp Pho 30	c cto e Leu	c cca 1 Pro	ttg Leu	ctg Leu 235	gag Glu	aag Lys	gtt Val	gto Val	gaq Glu 240	ı Ser	aac Asn	cgt Arg	cct Pro	ttg Leu 245		835

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ct Le	g at u Il	c at e II	tc ge le A.	la G	aa ga Lu As 50	ic gt	c ga l Gl	g gg u Gl	c ga y Gl 25	u Pr	t tt o Le	g ca u Gl	g ac n Th	c ct r Le 26	g gtt u Val	883	
gt Va	g aa l As	c to n Se	er I	te eq le Ar 65	gc aa gg Ly	g ac	c at r Il	c aa e Ly 27	s Va	c gt l Va	t go l Al	a gt a Va	g aa 1 Ly 27	s Se	c cct r Pro	931	· •
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Ala	Arg	Arq	345	y Glr 5	ı Ile	Arg	Arg	350	Ile	Ala	Asr	Thr	355	Ser	acc Thr	1171	
Trp	Asp	360	y Glu)	ı Lys		Glu	Glu 365	Arg	Leu	Ala	Lys	370	Ser	Gly	Gly	1219	
Ile	Ala 375	Val	. Ile	e Arg	gtt Val	Gly 380	Ala	Ala	Thr	Glu	Thr 385	Glu	Val	Asn	Asp	1267	
Arg 390	Lys	Leu	Arg	, Val	gaa Glu 395	Asp	Ala	Ile	Asn	Ala 400	Ala	Arg	Ala	Ala	Ala 405	1315	
Gln	Glu	Gly	Val	Ile 410	gct Ala	Gly	Gly	GIy	Ser 415	Ala	Leu	Val	Gln	Ile 420	Ala	1363	
Glu	Thr	Leu	Lys 425	Ala	tac Tyr	Ala	Glu	Glu 430	Phe	Glu	Gly	Asp	Gln 435	Lys	Val	1411	
Gly	Val	Arg 440	Ala	Leu	gct Ala	Thr	Ala 445	Leu	Gly	Lys	Pro	Ala 450	Tyr	Trp	Ile	1459	
Ala	tcc Ser 455	aac Asn	gca Ala	ggt Gly	ctt Leu	gac Asp 460	ggc Gly	tct Ser	gtt Val	Val	gtt Val 465	gca Ala	cgc Arg	act Thr	gct Ala	1507	

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-	_			-			-	gca Ala 510	-	_	-	-				1651
_		_	_	-	-		-	gaa Glu	-	-	-	-	-		-	1699
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Thr Asn Asp Gly Val Thr Ile Ala Arg Asp Ile Asp Leu Glu Asp Pro

Phe Glu Asn Leu Gly Ala Gln Leu Val Lys Ser Val Ala Val Lys Thr

Asn Asp Ile Ala Gly Asp Gly Thr Thr Thr Ala Thr Leu Leu Ala Gln

Ala Leu Ile Ala Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn Pro 100 105 110

Met Glu Leu Asn Lys Gly Ile Ser Ala Ala Ala Glu Lys Thr Leu Glu

Glu Leu Lys Ala Arg Ala Thr Glu Val Ser Asp Thr Lys Glu Ile Ala 135

Asn Val Ala Thr Val Ser Ser Arg Asp Glu Val Val Gly Glu Ile Val 150

Ala Ala Met Glu Lys Val Gly Lys Asp Gly Val Val Thr Val Glu

Glu Ser Gln Ser Ile Glu Thr Ala Leu Glu Val Thr Glu Gly Ile Ser 180 185 190

Phe Asp Lys Gly Tyr Leu Ser Pro Tyr Phe Ile Asn Asp Asn Asp Thr 195 200 205

Gln Gln Ala Val Leu Asp Asn Pro Ala Val Leu Leu Val Arg Asn Lys 210 215 220

Ile Ser Ser Leu Pro Asp Phe Leu Pro Leu Leu Glu Lys Val Val Glu 225 235 240

Ser Asn Arg Pro Leu Leu Ile Ile Ala Glu Asp Val Glu Gly Glu Pro 245 250 255

Leu Gln Thr Leu Val Val Asn Ser Ile Arg Lys Thr Ile Lys Val Val 260 265 270

Ala Val Lys Ser Pro Tyr Phe Gly Asp Arg Arg Lys Ala Phe Met Asp 275 280 285

Asp Leu Ala Ile Val Thr Lys Ala Thr Val Val Asp Pro Glu Val Gly 290 295 300

Ile Asn Leu Asn Glu Ala Gly Glu Glu Val Phe Gly Thr Ala Arg Arg 305 310 315 320

Ile Thr Val Ser Lys Asp Glu Thr Ile Ile Val Asp Gly Ala Gly Ser 325 330 335

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Asn Thr Asp Ser Thr Trp Asp Arg Glu Lys Ala Glu Glu Arg Leu Ala 355 360 365

Lys Leu Ser Gly Gly Ile Ala Val Ile Arg Val Gly Ala Ala Thr Glu 370 380

Thr Glu Val Asn Asp Arg Lys Leu Arg Val Glu Asp Ala Ile Asn Ala 385 390 395 400

Ala Arg Ala Ala Gln Glu Gly Val Ile Ala Gly Gly Gly Ser Ala
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Leu Val Gln Ile Ala Glu Thr Leu Lys Ala Tyr Ala Glu Glu Phe Glu
420 425 430

Gly Asp Gln Lys Val Gly Val Arg Ala Leu Ala Thr Ala Leu Gly Lys
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440
445

Pro Ala Tyr Trp Ile Ala Ser Asn Ala Gly Leu Asp Gly Ser Val Val 450 455 460

Val Ala Arg Thr Ala Ala Leu Pro Asn Gly Glu Gly Phe Asn Ala Ala

Thr Leu Glu Tyr Gly Asn Leu Ile Asn Asp Gly Val Ile Asp Pro Val 485 490 495

Lys Val Thr His Ser Ala Val Val Asn Ala Thr Ser Val Ala Arg Met 500 505 510

Val Leu Thr Thr Glu Ala Ser Val Val Glu Lys Pro Ala Glu Glu Ala 515 520 525

Ala Asp Ala His Ala Gly His His His His 530 535

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gct ttt gac cag gac gcc cgc gaa ggc att ctc cgg ggc gtt gac gct . 163 Ala Phe Asp Gln Asp Ala Arg Glu Gly Ile Leu Arg Gly Val Asp Ala 10 15 20

ctg gca aac gct gtc aag gta acc ctc ggc cca cgc ggc cgt aac gtg 211 Leu Ala Asn Ala Val Lys Val Thr Leu Gly Pro Arg Gly Arg Asn Val 25 30 35

gtt ctt gat aag gca ttc ggc gga cct ctg gtc acc aac gac ggt gtc 259
Val Leu Asp Lys Ala Phe Gly Gly Pro Leu Val Thr Asn Asp Gly Val
40 45 50

acc att gcc cgc gac atc gac ctt gag gat cct ttt gag aac ctc ggt 307 Thr Ile Ala Arg Asp Ile Asp Leu Glu Asp Pro Phe Glu Asn Leu Gly 55 60 65

gcg cag ctg gtg aag tcc gtt gct gtt aag acc aac gac atc gct ggt 355 Ala Gln Leu Val Lys Ser Val Ala Val Lys Thr Asn Asp Ile Ala Gly 70 75 80 85

gac ggc acc acg act gca act ctg ctt gct cag gca ctc att gct gaa 403 Asp Gly Thr Thr Thr Ala Thr Leu Leu Ala Gln Ala Leu Ile Ala Glu 90 95 100

ggc ctg cgc aac gtt gct gct ggc gca aac cca atg gag ctc aac aag 451

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547	gtt Val	acc	gct Ala	gtc Val	aac Asn 145	gca Ala	atc Ile	gaa Glu	Lys	acc Thr 140	gad Asp	tct Ser	g gto Val	Glu	a acc Thr 135	gca Ala
595	gaa Glu 165	atg Met	gcg Ala	gca Ala	gct Ala	gtt Val 160	atc Ile	gag Glu	ggc Gly	Val	gtt Val	gaa Glu	gat Asp	cgc Arg	Ser	tca Ser 150
643				tcc Ser							Gly					
691				gac Asp								Glu				
739				cag Gln 210												
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835				aac Asn												
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335

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Arg Gly Arg Asn Val Val Leu Asp Lys Ala Phe Gly Gly Pro Leu Val

Thr Asn Asp Gly Val Thr Ile Ala Arg Asp Ile Asp Leu Glu Asp Pro

Phe Glu Asn Leu Gly Ala Gln Leu Val Lys Ser Val Ala Val Lys Thr

Asn Asp Ile Ala Gly Asp Gly Thr Thr Thr Ala Thr Leu Leu Ala Gln

Ala Leu Ile Ala Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn Pro

Met Glu Leu Asn Lys Gly Ile Ser Ala Ala Ala Glu Lys Thr Leu Glu 115

Glu Leu Lys Ala Arg Ala Thr Glu Val Ser Asp Thr Lys Glu Ile Ala

Asn Val Ala Thr Val Ser Ser Arg Asp Glu Val Val Gly Glu Ile Val

145 ·

150

155

160

Ala Ala Met Glu Lys Val Gly Lys Asp Gly Val Val Thr Val Glu 165 170 175

Glu Ser Gln Ser Ile Glu Thr Ala Leu Glu Val Thr Glu Gly Ile Ser 180 185 190

Phe Asp Lys Gly Tyr Leu Ser Pro Tyr Phe Ile Asn Asp Asn Asp Thr 195 200 205

Gln Gln Ala Val Leu Asp Asn Pro Ala Val Leu Leu Val Arg Asn Lys 210 215 220

Ile Ser Ser Leu Pro Asp Phe Leu Pro Leu Leu Glu Lys Val Val Glu 225 230 235 240

Ser Asn Arg Pro Leu Leu Ile Ile Ala Glu Asp Val Glu Gly Glu Pro 245 250 255

Leu Gln Thr Leu Val Val Asn Ser Ile Arg Lys Thr Ile Lys Val Val 260 265 270

Ala Val Lys Ser Pro Tyr Phe Gly Asp Arg Arg Lys Ala Phe Met Asp 275 280 285

Asp Leu Ala Ile Val Thr Lys Ala Thr Val Val Asp Pro Glu Val Gly 290 295 300

Ile Asn Leu Asn Glu Ala Gly Glu Glu Val Phe Gly Thr Ala Arg Arg 305 310 315 320

Ile Thr Val Ser Lys Asp Glu Thr Ile Ile Val Asp Gly Ala Gly Ser 325 330 335

Ala Glu Asp Val Glu Ala Arg Arg Gly Gln Ile Arg Arg Glu Ile Ala 340 345 350

Asn Thr Asp Ser Thr Trp Asp Arg Glu Lys Ala Glu Glu Arg Leu Ala 355 360 365

Lys Leu Ser Gly Gly Ile Ala Val Ile Arg Val Gly Ala Ala Thr Glu 370 380

Thr Glu Val Asn Asp Arg Lys Leu Arg Val Glu Asp Ala Ile Asn Ala 385 390 395 400

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- acc att gag gct gct gcc cgc tct gag ttc ggc aag ggc tct gca cgt 163
 Thr Ile Glu Ala Ala Val Arg Ser Glu Phe Gly Lys Gly Ser Ala Arg
 10 15 20
- cgt gca cgc gtt gct ggc cag atc cct gct gtt gtt tac ggc gca gat 211 Arg Ala Arg Val Ala Gly Gln Ile Pro Ala Val Val Tyr Gly Ala Asp 25 30 35
- gtt gag tcc aac ctg cac gtc acc atc gac cac cgc acc ttc gct gcg 259
 Val Glu Ser Asn Leu His Val Thr Ile Asp His Arg Thr Phe Ala Ala
 40 45 50
- ctg gtt cgc cag gaa ggc gta aac gct gtt ctt gag ctc gac atc gag 307 Leu Val Arg Gln Glu Gly Val Asn Ala Val Leu Glu Leu Asp Ile Glu 55 60 65
- ggc cag aag cag ctc acc atg atc aag cac atc gac cag aac gtg ctg 355 Gly Gln Lys Gln Leu Thr Met Ile Lys His Ile Asp Gln Asn Val Leu 70 75 80 85
- acc ttc cac atc gac cac ttg gac ctg ctt gcc att aag cgc ggc gaa 403
 Thr Phe His Ile Asp His Leu Asp Leu Leu Ala Ile Lys Arg Gly Glu
 90 95 100
- aag gtt gag gtt gac gtt cca gtt atc gtc gag ggc gag cca gct cca 451 Lys Val Glu Val Asp Val Pro Val Ile Val Glu Gly Glu Pro Ala Pro 105 110 115
- ggc acc atg tgg gtt cag gat gct gac acc atc aag gtt gag gct gac 499
 Gly Thr Met Trp Val Gln Asp Ala Asp Thr Ile Lys Val Glu Ala Asp
 120 125 130
- gtt ctg tcc atc cct gaa gag ttc acc gtt tcc atc gaa ggc ctt gag 547 Val Leu Ser Ile Pro Glu Glu Phe Thr Val Ser Ile Glu Gly Leu Glu 135 140 145
- ctc ggc gca cag atc acc gca gct gac atc aag ctc gag ggc gac acc 595 Leu Gly Ala Gln Ile Thr Ala Ala Asp Ile Lys Leu Glu Gly Asp Thr 150 165
- acc ctg gtt gag gat cct gag acc ctc atc gtc aac atc gtt ctc cca 643
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185 190 195

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Arg Thr Phe Ala Ala Leu Val Arg Gln Glu Gly Val Asn Ala Val Leu 50 55 60

Glu Leu Asp Ile Glu Gly Gln Lys Gln Leu Thr Met Ile Lys His Ile 65 70 75 80

Asp Gln Asn Val Leu Thr Phe His Ile Asp His Leu Asp Leu Leu Ala 85 90 95

Ile Lys Arg Gly Glu Lys Val Glu Val Asp Val Pro Val Ile Val Glu 100 105 110

Gly Glu Pro Ala Pro Gly Thr Met Trp Val Gln Asp Ala Asp Thr Ile 115 120 125

Lys Val Glu Ala Asp Val Leu Ser Ile Pro Glu Glu Phe Thr Val Ser 130 135 140

Ile Glu Gly Leu Glu Leu Gly Ala Gln Ile Thr Ala Ala Asp Ile Lys 145 150 155 160

Leu Glu Gly Asp Thr Thr Leu Val Glu Asp Pro Glu Thr Leu Ile Val 165 170 175

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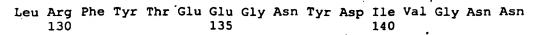
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acc cct aag acc tcc cgc cac cag gas ggc ttc ggc tcc cac acc ttc Thr Pro Lys Thr Ser Arg His Gln Asp Gly Phe Gly Ser His Thr Phe 200 205 cag tgg atc aac gct gaa ggt aag cca gtt tgg gtt aag tac cac ttc Gln Trp Ile Asn Ala Glu Gly Lys Pro Val Trp Val Lys Tyr His Phe 220 220 aag acc cgc cag ggc tgg gat tgc ttc acc gat gca gaa gca aca acg Lys Thr Arg Gln Gly Trp Asp Cys Phe Thr Asp Ala Glu Ala Ala Lys 240 gtt gca ggc gag aac gct gac tac cag ggc gaa gac ctc tac aac gct Val Ala Gly Glu Asn Ala Asp Tyr Gln Arg Glu Asp Leu Tyr Asn Ala 250 255 260 att gaa aac ggc gac ttc cca atc tgg gac gtc aag gtt cag atc atg Ile Glu Asn Gly Asp Phe Pro Ile Trp Asp Val Lys Val Gln Ile Met 265 270 cct ttc gag gat gca gag aac tac cgc tgg aac cca ttc gac ctg acc Pro Phe Glu Asp Ala Glu Asn Tyr Arg Trp Asn Pro Phe Asp Leu Thr 280 285 aag acc tgg tcc cag aag gat tac cca ctg atc cag tcg ggt tac ttc Lys Thr Trp Ser Gln Lys Asp Tyr Pro Leu Ile Pro Val Gly Tyr Phe 300 atc ctg aac cgc aac cca cgc aac ttc ttc ggc tcg gac gt tac ttc Lys Thr Trp Ser Gln Lys Asp Pro Phe Ala Gln Ile Glu Gln Leu 315 gca ctg gat ca ggc aac atc gt cct gg gc ctg tcc cca gac Ala Leu Asn Arg Asn Pro Arg Asn Phe Phe Ala Gln Ile Glu Gln Leu 315 gca ctg gat cca ggc acc atc ttc gca tac ggc gc ctg tcc cca gac Ala Leu Asp Pro Gly Asn Ile Val Fro Gly Val Gly Leu Ser Pro Asp 330 acc atg ctc cag gca cgt atc ttc gca tac gct gac cag cag ctt 326 cgc atg gct ccag gca cgt atc ttc gca tac gct gac cag cag ctg Arg Met Leu Gln Ala Arg Ile Phe Ala Tyr Ala Asp Gln Gln Arg Tyr 345 cgc atc ggc gct aac acc acc cgc gac gt ccc acc gca acc acc acc acc acc acc acc																		
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Lys Thr Arg Gln Gly Trp Asp Cys Phe Thr Asp Ala Glu Ala Ala Lys 245 gtt gca ggc gag aac gct gac tac cag cgc gaa gac ctc tac aac gct Val Ala Gly Glu Asn Ala Asp Tyr Gln Arg Glu Asp Leu Tyr Asn Ala 250 att gaa aac ggc gac ttc cca atc tgg gac gtc aag gtt cag atc atg Ile Glu Asn Gly Asp Phe Pro Ile Trp Asp Val Lys Val Gln Ile Met 265 cct ttc gag gat gca gag aac tac cgc tgg aac cca ttc gac ctg acc Pro Phe Glu Asp Ala Glu Asn Tyr Arg Trp Asn Pro Phe Asp Leu Thr 280 aag acc tgg tcc cag aag gat tac cca ctg atc cca gtc ggt tac ttc Lys Thr Trp Ser Gln Lys Asp Tyr Pro Leu Ile Pro Val Gly Tyr Phe 300 atc ctg aac cgc aac cac cgc aac tt ttc gct cag atc gag cag ctt Ile Leu Asn Arg Asn Pro Arg Asn Phe Phe Ala Glu Ile Glu Gln Leu 315 gca ctg gat cca ggc aac atc gtt cct ggc gtc ggc ctg tcc cca gac Ala Leu Asp Pro Gly Asn Ile Val Pro Gly Val Gly Leu Ser Pro Asp 330 cgc atg gat cca ggc aac atc gtt cct ggc gtc ggc ctg tcc cca gac Ala Leu Asp Pro Gly Asn Ile Val Pro Gly Val Gly Leu Ser Pro Asp 330 cgc atg gat cca ggc atc ttc gca tac gct gac cag cag ct 1109 Arg Met Leu Gln Ala Arg Ile Phe Ala Tyr Ala Asp Gln Gln Arg Tyr 345 cgc atc ggc gct aac tac cgc gac ctg cca gtg aac cgt caa atc aac Arg Ile Gly Ala Asn Tyr Arg Asp Leu Pro Val Asn Arg Pro Ile Asn 375 gag gtc aac acc tac agc cgc gaa ggt tcc atg cag cag cag cag Clu Val Asn Thr Tyr Ser Arg Glu Gly Ser Met Gln Tyr Ile Phe Asp 380 gct gag ggc gag cct tcc tac agc cct aac gac gac gac gac Glu Val Asn Thr Tyr Ser Arg Glu Gly Ser Met Gln Tyr Ile Phe Asp 380 gct gag ggc gag cct tcc tac agc cct aac cac cac cac cac cac cac cac ca		cag Gln	tgg Tr	g at	c aa e As	n Al	a Gl	a ggt u Gly	t aaq Y Lys	g cca s Pro	o Va	l Tr	g gt p Va	t aad 1 Ly:	g ta s Ty	r Hi	s Phe	725
Val Ala Gly Glu Asn Ala Asp Tyr Gln Arg Glu Asp Leu Tyr Asn Ala 250 att gaa aac ggc gac ttc cca atc tgg gac gtc aag gtt cag atc atg 11e Glu Asn Gly Asp Phe Pro Ile Trp Asp Val Lys Val Gln Ile Met 265 cct ttc gag gat gca gag aac tac cgc tgg aac cca ttc gac ctg acc Pro Phe Glu Asp Ala Glu Asn Tyr Arg Trp Asn Pro Phe Asp Leu Thr 280 aag acc tgg tcc cag aag gat tac cca ctg atc cca gtc ggt tac ttc Lys Thr Trp Ser Gln Lys Asp Tyr Pro Leu Ile Pro Val Gly Tyr Phe 300 atc ctg aac cgc aac cca cgc aac ttc ttc gct cag atc gag cag ctt 1013 atc ctg aac cgc aac cca cgc aac ttc ttc gct cag atc gag cag ctt 1013 Ile Leu Asn Arg Asn Pro Arg Asn Phe Phe Ala Gln Ile Glu Gln Leu 315 gca ctg gat cca ggc ac at cgt cct ggc gtc ggc ctg tcc cca gac Ala Leu Asp Pro Gly Asn Ile Val Pro Gly Val Gly Leu Ser Pro Asp 330 cgc atg ctc cag gca cgt atc ttc gca tac gct gac cag cag cgt tac Ala Leu Gln Ala Arg Ile Phe Ala Tyr Ala Asp Gln Gln Arg Tyr 350 cgc atc ggc gct aac tac cgc gac ctg cca gtg aac cgt cag cag cag ttc and Sat		aag Lys	Thr	c cge	Gl	n Gl	c tg y Tr	g gat o Asp	tgo Cys	Phe	Thi	c ga c As _l	t gca p Ala	a gaa a Glu	ı Ala	a Ala	a aag a Lys	773
Cot tite gag gat gea gag aac tac ege tgg aac cea tite gac etg gat aac ace tite gag gat gea gag gat tac cea cege tgg aac cea tite gac etg gat gea gag ace tgg tac tite gag gat gea gag gat tac cea cea gite ggt tac tite gag ace tgg tac etg gat ace cea gite ggt tac tite gat cea gat gat cea gat gat etg shows a solution of the following shows a soluti		gtt Val	gca Ala	Gly	/ Glu	g aad u Asi	c gci n Ala	gac Asp	Tyr	Gln	g cgo Arg	gaa g Glu	a gad u Ası	D Lei	ı Tyı	c aad	c gct n Ala	821
Pro Phe Glu Asp Ala Glu Asn Tyr Arg Trp Asn Pro Phe Asp Leu Thr 295 aag acc tgg tcc cag aag gat tac cca ctg atc cca gtc ggt tac ttc lys Thr Trp Ser Gln Lys Asp Tyr Pro Leu Ile Pro Val Gly Tyr Phe 300 atc ctg aac cgc aac cca cgc aac ttc ttc gct cag atc gag cag ctt lle Leu Asn Arg Asn Pro Arg Asn Phe Phe Ala Gln Ile Glu Gln Leu 315 gca ctg gat cca ggc aac atc gtt cct ggc ggc ctg tcc cca gac lof1 Ala Leu Asp Pro Gly Asn Ile Val Pro Gly Val Gly Leu Ser Pro Asp 330 cgc atg ctc cag gca cgt atc ttc gca tac gct gac cag cag cgt tac ll09 Arg Met Leu Gln Ala Arg Ile Phe Ala Tyr Ala Asp Gln Gln Arg Tyr 345 cgc atc ggc gct aac tac cgc gac ctg cca gt aac cgt ca acc gc aac gac ggt lle Gly Ala Asn Tyr Arg Asp Leu Pro Val Asn Arg Pro Ile Asn 360 gag gtc aac acc tac agc cgc gaa ggt tcc atg cag tac atc ttc gac Glu Val Asn Thr Tyr Ser Arg Glu Gly Ser Met Gln Tyr Ile Phe Asp 380 gct gag ggc gag cct tcc tac agc cct aac cgc tac gac aag ggc gca Ala Glu Gly Glu Pro Ser Tyr Ser Pro Asn Arg Tyr Asp Lys Gly Ala 395 ggc tac ctg gat aac ggt acg gat tcc tcc tac agc cac cac acc acc tcc tac Gly Tyr Leu Asp Asn Gly Thr Asp Ser Ser Ser Asn His Thr Ser Tyr		att Ile	Glu	Asr	ggo Gly	c gad y Asp	tto Phe	Pro	Ile	tgg Trp	gac Asp	gto Val	Llys	Val	caç Glr	g ato	e Met	869
Lys Thr Trp Ser Gln Lys Asp Tyr Pro Leu Ile Pro Val Gly Tyr Phe 300 atc ctg aac cgc aac cca cgc aac ttc ttc gct cag atc gag cag ctt Ile Leu Asn Arg Asn Pro Arg Asn Phe Phe Ala Gln Ile Glu Gln Leu 315 azo		Pro					Glu	Asn				Asn	Pro				Thr	917
Ile Leu Asn Arg Asn Pro Arg Asn Phe Phe Ala Gln Ile Glu Gln Leu 325 gca ctg gat cca ggc aac atc gtt cct ggc gtc ggc ctg tcc cca gac Ala Leu Asp Pro Gly Asn Ile Val Pro Gly Val Gly Leu Ser Pro Asp 330 cgc atg ctc cag gca cgt atc ttc gca tac gct gac cag cag cgt tac Arg Met Leu Gln Ala Arg Ile Phe Ala Tyr Ala Asp Gln Gln Arg Tyr 345 cgc atc ggc gct aac tac cgc gac ctg cca gtg aac cgt cca atc aac Arg Ile Gly Ala Asn Tyr Arg Asp Leu Pro Val Asn Arg Pro Ile Asn 360 gag gtc aac acc tac agc cgc gaa ggt tcc atg cag tac atc ttc gac Glu Val Asn Thr Tyr Ser Arg Glu Gly Ser Met Gln Tyr Ile Phe Asp 380 gct gag ggc gag cct tcc tac agc cct aac cgc tac gac aag ggc gac Ala Glu Gly Glu Pro Ser Tyr Ser Pro Asn Arg Tyr Asp Lys Gly Ala 395 ggc tac ctg gat aac ggt acg gat tcc tcc tcc aac cac acc tcc tac Gly Tyr Leu Asp Asn Gly Thr Asp Ser Ser Ser Asn His Thr Ser Tyr		aag Lys	acc Thr	tgg Trp	Ser	Gln	Lys	gat Asp	tac Tyr	cca Pro	Leu	Ile	cca Pro	gtc Val	ggt Gly	Tyr	Phe	965
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Glu Val Asn Thr Tyr Ser Arg Glu Gly Ser Met Gln Tyr Ile Phe Asp 380 385 390 gct gag ggc gag cct tcc tac agc cct aac cgc tac gac aag ggc gca Ala Glu Gly Glu Pro Ser Tyr Ser Pro Asn Arg Tyr Asp Lys Gly Ala 395 400 405 ggc tac ctg gat aac ggt acg gat tcc tcc tcc aac cac acc tcc tac Gly Tyr Leu Asp Asn Gly Thr Asp Ser Ser Ser Asn His Thr Ser Tyr		Arg	atc Ile	ggc. Gly	gct Ala	aac Asn	Tyr	cgc Arg	gac Asp	ctg Leu	cca Pro	Val	aac Asn	cgt Arg	cca Pro	atc Ile	Asn .	1157
Ala Glu Gly Glu Pro Ser Tyr Ser Pro Asn Arg Tyr Asp Lys Gly Ala 395 400 405 ggc tac ctg gat aac ggt acg gat tcc tcc tcc aac cac acc tcc tac Gly Tyr Leu Asp Asn Gly Thr Asp Ser Ser Ser Asn His Thr Ser Tyr		gag (Glu '	gtc Val	aac Asn	acc Thr	Tyr	agc Ser	cgc Arg	gaa Glu	Gly	Ser	atg Met	cag Gln	tac Tyr	atc Ile	Phe	gac Asp	1205
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		ggc t Gly 1	Cyr :	Leu	gat Asp	aac Asn	ggt Gly	Thr A	Asp :	tcc Ser	tcc Ser	tcc Ser	aac Asn	His	acc Thr	tcc Ser	tac Tyr	1301

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Thr Glu E	cca cgc g Pro Arg V 190	itc tac ga al Tyr As	ac tac to sp Tyr Ti 495	gg aac aac rp Asn Asi	c gtt gat on Val Asp (gag aac ctc Glu Asn Leu	1541
ggc gct c Gly Ala A 505	gc gtc a rg Val L	ag gag ct ys Glu Le 51	u Tyr Le	c cag aaq u Gln Lys	g aag gct t s Lys Ala 515	caagtccttc	1590
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Ser Glu As	sn Ile Se 85	r Ala Thr	Ala Gly	y Pro Gln	Gly Pro As	sn Val Leu	
Asn Asp Il 50	e His Le	u Ile Glu 55		Ala His	Phe Asn Ai	rg Glu Asn	
Val Pro Gl 65	u Arg Ilo	e Pro His 70	Ala Lys	Gly His	Gly Ala Ph	ne Gly Glu 80	
Leu His Il	e Thr Glu 85	a Asp Val	Ser Glu	Tyr Thr 90	Lys Ala As	p Leu Phe 95	
Gln Pro Gl	y Lys Val	Thr Pro	Leu Ala 105	Val Arg	Phe Ser Th		
Gly Glu Gli 115	n Gly Ser	Pro Asp	Thr Trp	Arg Asp	Val His Gl 125	y Phe Ala	



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His Ser Gln Lys Arg Leu Asn Lys Asn Gly Leu Arg Asp Ala Asp Met 165 170 175

Gln Trp Asp Phe Trp Thr Arg Ala Pro Glu Ser Ala His Gln Val Thr 180 185 190

Tyr Leu Met Gly Asp Arg Gly Thr Pro Lys Thr Ser Arg His Gln Asp 195 200 205

Gly Phe Gly Ser His Thr Phe Gln Trp Ile Asn Ala Glu Gly Lys Pro 210 215 220

Val Trp Val Lys Tyr His Phe Lys Thr Arg Gln Gly Trp Asp Cys Phe 225 230 235 240

Thr Asp Ala Glu Ala Ala Lys Val Ala Gly Glu Asn Ala Asp Tyr Gln
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Asp Val Lys Val Gln Ile Met Pro Phe Glu Asp Ala Glu Asn Tyr Arg 275 280 285

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Phe Ala Gln Ile Glu Gln Leu Ala Leu Asp Pro Gly Asn Ile Val Pro 325 330 335 _

Gly Val Gly Leu Ser Pro Asp Arg Met Leu Gln Ala Arg Ile Phe Ala 340 345 350

Tyr Ala Asp Gln Gln Arg Tyr Arg Ile Gly Ala Asn Tyr Arg Asp Leu 355 360 365

Pro Val Asn Arg Pro Ile Asn Glu Val Asn Thr Tyr Ser Arg Glu Gly 370 375 380

Ser Met Gln Tyr Ile Phe Asp Ala Glu Gly Glu Pro Ser Tyr Ser Pro 385 390 395 400

Asn Arg Tyr Asp Lys Gly Ala Gly Tyr Leu Asp Asn Gly Thr Asp Ser 405 410 415

Ser Ser Asn His Thr Ser Tyr Gly Gln Ala Asp Asp Ile Tyr Val Asn 420 425 430

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get geg att ttg eeg gtg tgg etg etg ett gea eeg ege gat tae etg

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			gtç Val		Ala					Ile					Val	1843
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- Leu Trp Ile Ile Leu Gly Val Ile Phe Ala Gly Ala Val Gln Asp Tyr 165 170 175
- Leu Val Leu Trp Val Ser Thr Arg Arg Gly Arg Ser Leu Gly Gln 180 185 190
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- Pro Arg Asp Tyr Leu Ser Thr Phe Met Lys Ile Gly Val Ile Gly Leu 325 330 335
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- Phe Val Ala Met Met Ala Leu Ile Thr Ala Val Ile Leu Asp Arg His
 420 425 430
- Leu Tyr Phe Ser Met Asn Ala Pro Leu Ala Leu Thr Gly Gly Asp Pro 435 440 445
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- Ile Thr Pro Glu Gln Leu Ser Glu Ala Ala Glu Ser Val Gly Glu Ser 465 470 475 480
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- Ser Glu Ile Leu Ser Gly Phe Ile Gly Gly Ala Gly Met Lys Ala Phe 500 505 510
- Trp Tyr His Phe Ala Ile Met Phe Glu Ala Leu Phe Ile Leu Thr Thr 515 520 525
- Val Asp Ala Gly Thr Arg Val Ala Arg Phe Met Met Thr Asp Thr Leu 530 535 540
- Gly Asn Val Pro Gly Leu Arg Arg Phe Lys Asp Pro Ser Trp Thr Val 545 550 555 560

Gly Asn Trp Ile Ser Thr Val Phe Val Cys Ala Leu Trp Gly Ala Ile 565 570 575

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Pro Leu Phe Gly Ile Ala Asn Gln Leu Leu Ala Ala Ile Ala Leu Ala 595 600 605

Leu Val Leu Val Val Val Lys Lys Gly Leu Tyr Lys Trp Ala Trp 610 615 620

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Ser Trp Gln Lys Ile Phe His Ser Asp Pro Ala Ile Gly Tyr Trp Ala 645 650 655

Gln Asn Ala Asn Phe Arg Asp Ala Lys Ser Gln Gly Leu Thr Glu Phe
660 665 670

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gct gaa atc atg gag ctt gac cag tcc aag gac cac gca acc tac gtt Ala Glu Ile Met Glu Leu Asp Gln Ser Lys Asp His Ala Thr Tyr Val 25 30 35	211
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Ą	at sp	tcc Ser	at : Il	c t e T	at (atc Ile 90	cac His	ccc Pro	caç Glr	g gg n Gl	уG	aa q ln G 95	ggc	cga Arg	gga Gly	a at	le	ggc Gly 100	ggc	403
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C. H.	15	gaa Glu 135	Sei	g aa c Ly	ag g /s G	gc	ttc Phe	gtg Val 140	aag Lys	gto Val	g gg	јс а .y Т	hr	atg Met 145	cac His	ca Gl	a a n N	itg let	gca Ala	547
aç Ai 15	. g .	atg Met	Pro	ta Ty	r G	тÀ	gag Glu 155	atg Met	gaa Glu	gga Gly	a ca / Gl	n Ti	gg (rp 1	cgc Arg	gat Asp	tg Cy	t g s A	at	ctg Leu 165	595
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				20					lu I	25						30		•	•	
Thr	Т	yr G	35	Thr	Sei	r GI	Ly P	ro T	hr 1 40	rp	Asp	Glr	n Pl	ne S	er (Gln	Se	r I	ys	
Ile	Me	et A 50	ge	Thr	Val	. Ме	et V	al A 55	la V	'al	Glu	Asn		sn A 50	sp 1	Pro	As	p P	he	
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His	Gl	y V	al '	Val	Glu 85	As	p Se	r I	le T	yr :	Ile 90	His	Pr	o G	ln G	ly		n G	ly	
Arg	G1	у І	le (31 <i>y</i> 100	Gly	Al	a Le	u Le	u A:	sp <i>1</i> 05	Ala	Leu	11	e Tì		yr 10	Cys	s G.	lu	
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120

125

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Thr Trp Asp Gln Phe Ser Gln Ser Lys Ile Met Asp Thr Val Met Val
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1le Tyr Ile His Pro Gln Gly Gln Gly Arg Gly Ile Gly Gly Ala Leu

70

75

80

85

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Gly Trp Val Ser Ala Ala Pro Ile Ser Ser Arg Gln Val Phe His Gly 50 55 60

Val Val Glu Asp Ser Ile Tyr Ile His Pro Gln Gly Gln Gly Arg Gly 65 70 75 80

Ile Gly Gly Ala Leu Leu Asp Ala Leu Ile Thr Tyr Cys Glu Ser Asn 85 90 95

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tat Tyr	Pro	c ato	c gte e Vai 2!	l Th	t gto	g gaa l Gli	a gat 1 Asi	t to Sei 30	: Lev	a ggo a Gly	c gad y Asp	acc Thr	cac His	Asp	ttc Phe	211
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g	gc	acc Thr	: са Ні 20	s Hi	ic ga .s Gl	ig gt .u Va	t gt 1 Va	g tc 1 Se 20	r Se	c at	t gg e Gl	c att y Ile	t tca Ser 210	r Ar	c cti	t ggt u Gly	739
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agc tcc atc acc of Ser Ser Ile Thr A 440	gat gtg gat gct asp Val Asp Ala 445	acc gag att tca cgt ttc Thr Glu Ile Ser Arg Phe 450	gat ggc 1459 Asp Gly
cca gaa gta gaa g Pro Glu Val Glu G 455	aa acc atc aca lu Thr Ile Thr 460	gtc aat gac aac ggc gtg Val Asn Asp Asn Gly Val 465	gct tcc 1507 Ala Ser
att tcc atc aag a Ile Ser Ile Lys I 470	ta ctc ggc ggc o le Leu Gly Gly v 475	gtt acc gtc gag cac aca Val Thr Val Glu His Thr 480	att 1552 Ile
tagttaccat tttggt	jctg gtg		1575
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	•		
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Val Asp Arg Gly As 20	n Tyr Pro Ile V	al Thr Val Glu Asp Ser 25 30	Leu Gly
Asp Thr His Asp Ph	e Ile Pro Ser Va 40	al Val Ala Leu Lys Ala . 45	Asp Ārg
Ile Val Ala Gly Try 50	Asp Ala Ile G	lu Val Gly Gln Asp His 60	Pro Ser
Phe Val Arg Ser Phe	E Lys Arg Leu Le 70	eu Ser Glu Pro Asn Val : 75	Chr Glu 80
Ala Thr Pro Val Tyr	Leu Gly Asp Hi	s Val His Pro Leu Gly P	ala Val

Leu Glu Ala Phe Ala Glu Asn Val Val Thr Ala Leu Arg Ala Phe Gln

Thr Gln Leu Gly Asp Thr Ser Pro Ile Glu Val Val Ile Gly Val Pro 115 120 125

105

100

- Ala Asn Ser His Ser Ala Gln Arg Leu Leu Thr Met Ser Ala Phe Ser 130 135 140
- Ala Thr Gly Ile Thr Val Val Gly Leu Val Asn Glu Pro Ser Ala Ala . 150 155 160
- Ala Phe Glu Tyr Thr His Arg His Ala Arg Thr Leu Asn Ser Lys Arg 165 170 175
- Gln Ala Ile Val Val Tyr Asp Leu Gly Gly Gly Thr Phe Asp Ser Ser 180 185 190
- Leu Ile Arg Ile Asp Gly Thr His His Glu Val Val Ser Ser Ile Gly 195 200 205
- Ile Ser Arg Leu Gly Gly Asp Asp Phe Asp Glu Ile Leu Leu Gln Cys 210 220
- Ala Leu Lys Ala Ala Gly Arg Gln His Asp Ala Phe Gly Lys Arg Ala 225 230 235 240
- Lys Asn Thr Leu Leu Asp Glu Ser Arg Asn Ala Lys Glu Ala Leu Val 245 250 255
- Pro Gln Ser Arg Arg Leu Val Leu Glu Ile Gly Asp Asp Ile Thr 260 265 270
- Val Pro Val Asn Lys Phe Tyr Glu Ala Ala Thr Pro Leu Val Glu Lys 275 280 285
- Ser Leu Ser Ile Met Glu Pro Leu Ile Gly Val Asp Asp Leu Lys Asp 290 295 300
- Ser Asp Ile Ala Gly Ile Tyr Leu Val Gly Gly Gly Ser Ser Leu Pro 305 310 315 320
- Leu Val Ser Arg Leu Leu Arg Glu Arg Phe Gly Arg Arg Val His Arg 325 330 335
- Ser Pro Phe Pro Ser Gly Ser Thr Ala Val Gly Leu Ala Ile Ala Ala 340 345 350
- Asp Pro Ser Ser Gly Phe His Leu Arg Asp Arg Val Ala Arg Gly Ile 355 360 365
- Gly Val Phe Arg Glu His Asp Ser Gly Arg Ala Val Ser Phe Asp Pro 370 380
- Leu Ile Ala Pro Asp Thr Asp Ser Ala Thr Val Ala Lys Arg Cys Tyr 385 390 395 400
- Lys Ala Val His Asn Ile Gly Trp Phe Arg Phe Val Glu Tyr Ser Thr 405 410 415
- Val Ser Glu Asp Gly Ser Pro Gly Asp Ile Ser Leu Leu Ser Glu Ile 420 425 430

Lys Ile Pro Phe Asp Ser Ser Ile Thr Asp Val Asp Ala Thr Gru Ile 435 440 445

Ser Arg Phe Asp Gly Pro Glu Val Glu Glu Thr Ile Thr Val Asn Asp 450 455 460

Asn Gly Val Ala Ser Ile Ser Ile Lys Ile Leu Gly Gly Val Thr Val 465 470 475 480

Glu His Thr Ile

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 <223> FRXA01345
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- ttccactgca cagcccgaaa atgctgctag ggtcaagttc atg cgt ttt gga ctt 115 Met Arg Phe Gly Leu 1 5
- gac ttg gga act acc cgc aca atc gcg gcc gcc gtg gac cgc gga aac $$ 163 Asp Leu Gly Thr Thr Arg Thr Ile Ala Ala Ala Val Asp Arg Gly Asn $$ 10 $$ 15 $$ 20
- tat ccc atc gtc act gtg gaa gat tct tta ggc gac acc cac gat ttc 211
 Tyr Pro Ile Val Thr Val Glu Asp Ser Leu Gly Asp Thr His Asp Phe
 25 30 35
- att cca tct gtg gtg gcc ctc aag gca gat agg att gtc gcg ggt tgg 259
 Ile Pro Ser Val Val Ala Leu Lys Ala Asp Arg Ile Val Ala Gly Trp
 40 45 50
- gat gct att gag gtt ggg cag gac cac cct tcc ttc gta cgt tct ttc 307 Asp Ala Ile Glu Val Gly Gln Asp His Pro Ser Phe Val Arg Ser Phe 55 60 65
- aaa cgc cta ctc tct gaa ccc aat gtc acg gaa gcc acc ccg gtc tac 355
 Lys Arg Leu Leu Ser Glu Pro Asn Val Thr Glu Ala Thr Pro Val Tyr
 70 75 80 85
- ttg ggc gat cat gta cac cct ttg ggc gcc gtc ctg gag gct ttt gcg 403 Leu Gly Asp His Val His Pro Leu Gly Ala Val Leu Glu Ala Phe Ala 90 95 100
- gaa aac gtg gtc act gcg ctg cgt gca ttt cag acg caa ttg gga gat 451 Glu Asn Val Val Thr Ala Leu Arg Ala Phe Gln Thr Gln Leu Gly Asp 105 110 115

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gcc cag cg Ala Gln Ar 135	a ctg ctc a g Leu Leu Tl	ec atg tec or Met Ser 140	gcc ttc Ala Phe	age gee aca Ser Ala Thr 145	ggc atc acc Gly Ile Thr	547
gtt gtc gg Val Val Gl 150	t ttg gtc aa y Leu Val As 15	n Glu Pro	Ser Ala	gca gct ttc Ala Ala Phe 160	gag tac acc Glu Tyr Thr 165	595
cac cgc cac His Arg His	gee ege ac Ala Arg Th 170	c tta aac r Leu Asn	tcc aag Ser Lys 1 175	cgc caa gcc a Arg Gln Ala 1	atc gtg gtt Ile Val Val 180	643
tat gat tto Tyr Asp Leu	g gga ggc gg n Gly Gly Gl 185	a aca ttc y Thr Phe	gac tcc t Asp Ser S 190	tcg ctc atc o Ser Leu Ile <i>l</i>	egc atc gac Arg Ile Asp 195	691
ggc acc cac Gly Thr His 200	His Glu Va	t gtg tcc l Val Ser 205	tcc att o Ser Ile 6	ggc att tca c Gly Ile Ser A 210	gc ctt ggt rg Leu Gly	739
ggc gat gat Gly Asp Asp 215	ttc gat gaa Phe Asp Gli	atc ctc Ile Leu 220	ctc caa t Leu Gln C	gc gcg ctc a Cys Ala Leu I 225	ag gcc gca ys Ala Ala	787
ggc aga cag Gly Arg Gln 230	cac gat gco His Asp Ala 235	Phe Gly	Lys Arg A	ct aaa aac a la Lys Asn T 40	cg ctt ctc hr Leu Leu 245	835
gac gaa tcc Asp Glu Ser	cgc aac gcg Arg Asn Ala 250	aag gaa q Lys Glu <i>I</i>	gct ctt g Ala Leu V 255	tt ccg caa t al Pro Gln S	cc cgt cgc er Arg Arg 260	883
ttg gtt cta Leu Val Leu	gaa att ggc Glu Ile Gly 265	Asp Asp A	gac atc ad Asp Ile Th 170	cc gtt cca g nr Val Pro Va 27	al Asn Lys	931
ttc tac gag Phe Tyr Glu 280	gct gcc act Ala Ala Thr	ccc ctg g Pro Leu V 285	tg gaa aa al Glu Ly	aa too ttg to /s Ser Leu Se 290	cc atc atg er Ile Met	979
gaa ccc ctc Glu Pro Leu 295	atc ggc gtc Ile Gly Val	gat gat c Asp Asp L 300	tt aaa ga eu Lys As	t tcc gac at p Ser Asp Il 305	c gca ggc e Ala Gly	1027
atc tac ctt of Ile Tyr Leu V 310	gtt ggt gga Val Gly Gly 315	gga tcc to Gly Ser Se	eg ete ee er Leu Pr 32	o Leu Val Se	c agg ttg r Arg Leu 325	1075
ctc cgc gag c Leu Arg Glu A	arg Phe Gly 330	cgc cgt gt Arg Arg Va	c cac cge al His Arc 335	c tcc cca tt g Ser Pro Ph	c ccc tca e Pro Ser 340	1123

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ggt tcc act gcg gtg ggt ctg gcc atc gcg gct gac cct tcc tct ggt 1171 Gly Ser Thr Ala Val Gly Leu Ala Ile Ala Ala Asp Pro Ser Ser Gly 345 350 355

ttc cac cta agg gac cgc gtt gcg cga ggc atc ggt gtg ttc cgt gag 1219 Phe His Leu Arg Asp Arg Val Ala Arg Gly Ile Gly Val Phe Arg Glu 360 365 370

cac gat tct ggt cgt gcc gtg agc ttt gac ccg ctg atc gcc ccg gac 1267 His Asp Ser Gly Arg Ala Val Ser Phe Asp Pro Leu Ile Ala Pro Asp 375 380 385

<210> 26

<211> 389

<212> PRT

<213> Corynebacterium glutamicum

<400> 26

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Val Asp Arg Gly Asn Tyr Pro Ile Val Thr Val Glu Asp Ser Leu Gly
20 25 30

Asp Thr His Asp Phe Ile Pro Ser Val Val Ala Leu Lys Ala Asp Arg 35 40 45

Ile Val Ala Gly Trp Asp Ala Ile Glu Val Gly Gln Asp His Pro Ser 50 60

Phe Val Arg Ser Phe Lys Arg Leu Leu Ser Glu Pro Asn Val Thr Glu 65 70 75 80

Ala Thr Pro Val Tyr Leu Gly Asp His Val His Pro Leu Gly Ala Val 85 90 95

Leu Glu Ala Phe Ala Glu Asn Val Val Thr Ala Leu Arg Ala Phe Gln 100 105 110

Thr Gln Leu Gly Asp Thr Ser Pro Ile Glu Val Val Ile Gly Val Pro
115 120 125

Ala Asn Ser His Ser Ala Gln Arg Leu Leu Thr Met Ser Ala Phe Ser 130 135 140

Ala Thr Gly Ile Thr Val Val Gly Leu Val Asn Glu Pro Ser Ala Ala 145 150 155 160

Ala Phe Glu Tyr Thr His Arg His Ala Arg Thr Leu Asn Ser Lys Arg 165 170 175

Gln Ala Ile Val Val Tyr Asp Leu Gly Gly Gly Thr Phe Asp Ser Ser 180 185

Leu Ile Arg Ile Asp Gly Thr His His Glu Val Val Ser Ser Ile Gly
195 200 205

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Ile Ser Arg Leu Gly Gly Asp Asp Phe Asp Glu Ile Leu Leu Gln Cys 210

Ala Leu Lys Ala Ala Gly Arg Gln His Asp Ala Phe Gly Lys Arg Ala 240

Lys Asn Thr Leu Leu Asp Glu Ser Arg Asn Ala Lys Glu Ala Leu Val 255

Pro Gln Ser Arg Arg Leu Val Leu Glu Ile Gly Asp Asp Asp Ile Thr 260

Val Pro Val Asn Lys Phe Tyr Glu Ala Ala Thr Pro Leu Val Glu Lys 280

Ser Leu Ser Ile Met Glu Pro Leu Ile Gly Val Asp Asp Leu Lys Asp 300

Ser Asp Ile Ala Gly Ile Tyr Leu Val Gly Gly Gly Ser Ser Leu Pro 305

Leu Val Ser Arg Leu Leu Arg Glu Arg Phe Gly Arg Arg Val His Arg 335

Ser Pro Phe Pro Ser Gly Ser Thr Ala Val Gly Leu Ala Ile Ala Ala 340 345 350

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Gly Val Phe Arg Glu His Asp Ser Gly Arg Ala Val Ser Phe Asp Pro 370 375 380

Leu Ile Ala Pro Asp 385

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<213> Corynebacterium glutamicum

<220>

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<222> (101)..(1285)

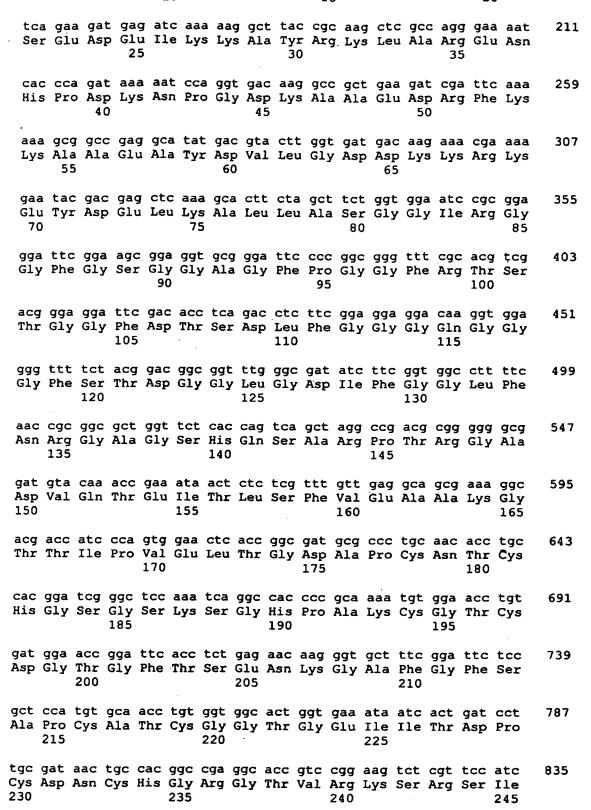
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tgg gca aat aag aac tat tac gca gac ctg ggg gtc tcc tcg tcc gct 163 Trp Ala Asn Lys Asn Tyr Tyr Ala Asp Leu Gly Val Ser Ser Ser Ala



														•		
ac Th	c gt r Va	g cg l Ar	t at g Il	c cc e Pr 25	o Thi	ggt Gly	gto Val	g gaa Glu	a gat 1 Asp 255	G13	a caq y Glr	g aaa n Lys	gtt Val	cgt Arg 260	ctt g Leu)	883
gc Al	a gg a Gl	c ca y Gl	a gg n Gl 26	A CT	a gca u Ala	a gga a Gly	cca Pro	aat Asn 270	Gly	aaa Lys	a cca s Pro	gcg Ala	ggc Gly 275	Asp	ctc Leu	931
tt Ph	t gto	g aa L Ly 28	s Va.	c cad l His	gtg Val	aaa Lys	aag Lys 285	gac Asp	gat Asp	gtg Val	ttc Phe	aca Thr 290	cgc Arg	gac Asp	ggc	979
ago Sei	2 aad 2 Asr 295	1 116	t tto	g ato 1 Ile	acc Thr	att Ile 300	ccc Pro	gtg Val	agc Ser	ttc Phe	agc Ser 305	gag Glu	ctg Leu	gct Ala	ttg Leu	1027
ggt Gly 310	, ст	gct Alé	att Ile	tct Ser	gtg Val 315	cca Pro	acg Thr	ctc Leu	aac Asn	aag Lys 320	cct Pro	gta Val	aaa Lys	ctc Leu	aag Lys 325	1075
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gtt Val	tct Ser	gtc Val 360	ccg Pro	aag Lys	aat Asn	Leu .	gat Asp 365	gac Asp	aac Asn	gct Ala	Ala	gaa Glu 370	gct Ala	ctc Leu	cgc Arg	1219
gca Ala	tat Tyr 375	gct Ala	gaa Glu	gca Ala	gaa Glu	act a Thr A 380	aat 1 Asn 3	tca Ser	ggt Gly	Phe	gat Asp 385	ccc (Pro 1	ege Arg	gct Ala	aac Asn	1267
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<212> PRT

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<400> 28

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Val Ser Ser Ser Ala Ser Glu Asp Glu Ile Lys Lys Ala Tyr Arg Lys
20 25 30

Leu Ala Arg Glu Asn His Pro Asp Lys Asn Pro Gly Asp Lys Ala Ala 35 40 45

Glu	Asp	Arg	Phe	Lys	Lys	Ala	Ala	Glu	Ala	Tyr	Asp	Val	Leu	GIY	Asp
	50					55				_	60			-	•

- Asp Lys Lys Arg Lys Glu Tyr Asp Glu Leu Lys Ala Leu Leu Ala Ser 65 70 75 80
- Gly Gly Ile Arg Gly Gly Phe Gly Ser Gly Gly Ala Gly Phe Pro Gly 85 90 95
- Gly Phe Arg Thr Ser Thr Gly Gly Phe Asp Thr Ser Asp Leu Phe Gly
 100 105 110
- Gly Gly Gly Gly Gly Phe Ser Thr Asp Gly Gly Leu Gly Asp Ile 115 120 125
- Phe Gly Gly Leu Phe Asn Arg Gly Ala Gly Ser His Gln Ser Ala Arg 130 135 140
- Pro Thr Arg Gly Ala Asp Val Gln Thr Glu Ile Thr Leu Ser Phe Val 145 150 155 160
- Glu Ala Ala Lys Gly Thr Thr Ile Pro Val Glu Leu Thr Gly Asp Ala 165 170 175
- Pro Cys Asn Thr Cys His Gly Ser Gly Ser Lys Ser Gly His Pro Ala 180 185 190
- Lys Cys Gly Thr Cys Asp Gly Thr Gly Phe Thr Ser Glu Asn Lys Gly 195 200 205
- Ala Phe Gly Phe Ser Ala Pro Cys Ala Thr Cys Gly Gly Thr Gly Glu 210 215 220
- Ile Ile Thr Asp Pro Cys Asp Asn Cys His Gly Arg Gly Thr Val Arg 225 230 235 240
- Lys Ser Arg Ser Ile Thr Val Arg Ile Pro Thr Gly Val Glu Asp Gly 245 250 255
- Gln Lys Val Arg Leu Ala Gly Gln Gly Glu Ala Gly Pro Asn Gly Lys 260 265 270
- Pro Ala Gly Asp Leu Phe Val Lys Val His Val Lys Lys Asp Asp Val 275 280 285
- Phe Thr Arg Asp Gly Ser Asn Ile Leu Ile Thr Ile Pro Val Ser Phe 290 295 300
- Ser Glu Leu Ala Leu Gly Gly Ala Ile Ser Val Pro Thr Leu Asn Lys 305 310 315 320
- Pro Val Lys Leu Lys Leu Pro Ala Gly Thr Pro Asp Gly Arg Thr Leu 325 330 335
- Arg Val Arg Gly Arg Gly Ile Glu Ala Arg Asp Ser Thr Gly Asp Leu 340 345 350

Leu Val Thr Val Gln Val Ser Val Pro Lys Asn Leu Asp Asp Asn Ala 355 360 365

Ala Glu Ala Leu Arg Ala Tyr Ala Glu Ala Glu Thr Asn Ser Gly Phe 370 380

Asp Pro Arg Ala Asn Trp Ala Gly Gln Asn Arg 385 390 395

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<212> DNA

<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (101)..(754)

<223> RXA02542

<400> 29

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gga atg ccc gac aat cct ggg gat cct gaa aat acc gat cca gag gca 163 Gly Met Pro Asp Asn Pro Gly Asp Pro Glu Asn Thr Asp Pro Glu Ala 10 15 20

acc tct gct gat cgt gct gag cag gca gct gaa gaa gca gct gcc cgc 211
Thr Ser Ala Asp Arg Ala Glu Gln Ala Ala Glu Glu Ala Ala Ala Arg
25 30 35

caa gcg gag gaa tct cca ttt gga cag gcc tca gag gaa gaa att tct 259 Gln Ala Glu Glu Ser Pro Phe Gly Gln Ala Ser Glu Glu Glu Ile Ser
40 45 50

cca gag ctc gaa gca gag atc aat gat ctt cta tca gat gtt gat cca 307 Pro Glu Leu Glu Ala Glu Ile Asn Asp Leu Leu Ser Asp Val Asp Pro 55 60 65

gat ttg gat ggc gat ggt gaa gtg tcc gct gta gaa aca cag ctt gcc 355
Asp Leu Asp Gly Asp Gly Glu Val Ser Ala Val Glu Thr Gln Leu Ala
70 80 85

gaa cgc act gag gat ctg cag cga gtc acc gct gag tac gcc aac tac 403 Glu Arg Thr Glu Asp Leu Gln Arg Val Thr Ala Glu Tyr Ala Asn Tyr 90 95 100

cgt cga cgt acc gag cgt gaa cgc cag ggc atc atc gac acc gca cgc 451 Arg Arg Arg Thr Glu Arg Glu Arg Gln Gly Ile Ile Asp Thr Ala Arg 105 110 115

gca ggt gtt gtt acc caa ctt ctg ccg ttg ctc gac gat ctt gac ctg 499 Ala Gly Val Val Thr Gln Leu Leu Pro Leu Leu Asp Asp Leu Asp Leu

	120	125		130	•
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gac aag o Asp Lys I 150	ctg atc aac at Leu Ile Asn Il 15	e ren era e	gga ttg aag gtg ily Leu Lys Val 160	ggaa too tto g . Glu Ser Phe G 1	gc 595 1y 65
gag atc g Glu Ile G	gc gaa gca tt ly Glu Ala Pho 170	c gat cca g e Asp Pro G	ag atc cac gaa lu Ile His Glu 175	gca gta cag g Ala Val Gln A 180	at 643 sp
ctc tca c Leu Ser G	ag ggt gat gto ln Gly Asp Val 185	L Lys Val L	tg gga acg gta eu Gly Thr Val 90	ctc cgc aag g Leu Arg Lys G 195	ga 691 ly
Tyr Arg L	tc ggc gac cgc eu Gly Asp Arg 00	gtc atc co Val Ile Ai 205	gc acc gca atg rg Thr Ala Met	gtc ctc att go Val Leu Ile G 210	gg 739 ly
gat cca ga Asp Pro Gl 215	ag gag agc tag Lu Glu Ser	agagact aag	ytctctta gtg		777
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Thr Asp Pro	o Glu Ala Thr 20	Ser Ala Asp 25	o Arg Ala Glu (Gln Ala Ala Gl	u
Glu Ala Ala 35	a Ala Arg Gln	Ala Glu Glu 40	Ser Pro Phe (Gly Gln Ala Šei 45	r
Glu Glu Glu 50	lle Ser Pro	Glu Leu Glu 55	Ala Glu Ile A 60	Asn Asp Leu Leu	1
Ser Asp Val 65	Asp Pro Asp 1	Leu Asp Gly	Asp Gly Glu V	al Ser Ala Val 80	
Glu Thr Gln	Leu Ala Glu A 85	Arg Thr Glu	Asp Leu Gln A	rg Val Thr Ala 95	
Glu Tyr Ala	Asn Tyr Arg A	arg Arg Thr 105	Glu Arg Glu A	rg Gln Gly Ile 110	
Ile Asp Thr 115	Ala Arg Ala G	ly Val Val 120		eu Pro Leu Leu 25	

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Asp Asp Leu Asp Leu Ala Glu Gln His Gly Asp Leu Asn Glu Gly Pro 130 135 140

Leu Lys Ser Leu Ser Asp Lys Leu Ile Asn Ile Leu Gly Gly Leu Lys
145 150 155 160

Val Glu Ser Phe Gly Glu Ile Gly Glu Ala Phe Asp Pro Glu Ile His 165 170 175

Glu Ala Val Gln Asp Leu Ser Gln Gly Asp Val Lys Val Leu Gly Thr 180 185 190

Val Leu Arg Lys Gly Tyr Arg Leu Gly Asp Arg Val Ile Arg Thr Ala 195 200 205

Met Val Leu Ile Gly Asp Pro Glu Glu Ser 210 215

<210> 31

<211> 1977

<212> DNA

<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (101)..(1954)

<223> RXN02543

<400> 31

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Met Gly Arg Ala Val

gga att gac ctt gga acc acc aac tct gtg gtt tcc gta ctt gaa ggc 163 Gly Ile Asp Leu Gly Thr Thr Asn Ser Val Val Ser Val Leu Glu Gly 10 15 20

ggc gag cca gta gtt atc gca aac gca gaa ggc tca cgc acc acc cct 211 Gly Glu Pro Val Val Ile Ala Asn Ala Glu Gly Ser Arg Thr Thr Pro 25 30 35

tcc gtc gtt gca ttc gca aag aac ggt gaa gtt cta gtc ggc cag tcc 259
Ser Val Val Ala Phe Ala Lys Asn Gly Glu Val Leu Val Gly Gln Ser
40 45 50

gct aag aac cag gcg gtc acc aac gtt gac cgc acc att cgc tcc gtc 307 Ala Lys Asn Gln Ala Val Thr Asn Val Asp Arg Thr Ile Arg Ser Val

aag cgc cac atc ggc acc gac tgg tcc gtt gct atc gat gac aag aac 355 Lys Arg His Ile Gly Thr Asp Trp Ser Val Ala Ile Asp Asp Lys Asn 75 80 85

tac acc tca cag gaa atc tcg gct cgt acc ctg atg aag ctg aag cgc 403

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	gtt Val	cct Pro	gca Ala 120	tac Tyr	ttc (Phe (gag (Glu <i>l</i>	nsp	tca Ser 125	cag Gln	cgc Arg	cag Gln	gca Ala	acc Thr 130	aag Lys	gaa Glu	gct Ala	499
	ggt Gly	cag Gln 135	atc Ile	gca Ala	ggc o Gly I	eu r	aac Asn 140	gtt Val	ctg Leu	cgt Arg	Ile	gtt Val 145	aac (Asn (gag Glu	cca Pro	acc Thr	547
	gcg Ala 150	gct Ala	gca (Ala)	ctt (Leu <i>l</i>	77 G T	ac g yr G 55	igc o	ctt Leu (gag Glu	ras (ggc Gly (gag (Glu (cag q Gln (gag (Glu (Sln	acc Thr 165	595
	att Ile	ctg Leu	gta t Val E	ine A	ac c sp L 70	tc g eu G	gt g ly G	ggc (Sly (TA.	acc t Thr H 175	tc (Phe A	gac (Asp (gtc t Val S	er I	eu :	cta Leu	643
	gag a Glu :	atc ([le (,	ac g sp G 85	gt gt ly Va	it gi	tt g al G	Tu A	tt d al A	ege g Arg A	ca a la T	icc t	er G	gc g ly A 95	at a	aac Asn	691
	gag d Glu I		ggt g Gly G 200	gc ga ly Aa	ac ga sp As	c to p Tr	P A	at c sp G 05	ag c ln A	gt a rg I	tc g le V	al A	ac to sp T:	gg c rp L	tg g eu V	jta Val	739
	gag a Glu L 2	ag t ys P 15	tc ca	ag to ln Se	c tc er Se	c aa r As 22	n Gi	gc a Ly I	tt g le A	ac c sp L	eu T	cc a hr L 25	ag ga ys As	ac aa sp Ly	ag a ys M	tg et	787
	gcc c Ala L 230	tg c eu G	ag co ln Ar	gt ct rg Le	g cgr u Arc 235	a GTI	g go u Al	a go a Al	et ga La Gi	ag aa lu Ly 24	/S Al	ca aa la Ly	ag at /s Il	c ga e Gl	u L	tg eu 45	835
	tcc to Ser Se	et to	cc ca ∍r Gl	n Se 25	- VT0	aac Asr	at n Il	c aa e As	n re	t cc u Pr i5	о Ту	c at	c ac e Th	c gt r Va 26	1 As	at sp	883
-	gca ga Ala As	c aa p Ly	ag aa /s As: 26:		a ctg D Leu	ttc Phe	tte	g ga ı Ası 27	ь ст	g ac u Th	c ct r Le	t tc u Se	c cg r Are 27!	g Al	c ga a Gl	ig .u	931
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	aac ca Asn Gli 29	1 14.	t gtt l Val	aag Lys	gac Asp	gct Ala 300	ggc	gtç Val	j tco Sei	gto Val	tco Ser 305	: Glu	j ato 1 Ile	gac Asp	ca Hi:	c s	1027
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Strong and ctg acc ggt ggg cgt gag cca aac aac aac ag ggt gtt aac cca 1123		•			320	325)
345 345 346 347 348 348 350 355 355 355 356 360 360 360 360 365 365 365 360 365 360 365 360 365 360 365 360 365 360 365 360 365 360 365 360 365 360 365 360 365 365 360 365 365 360 365 365 360 365 365 365 366 365 366 365 366 365 366 366	var Lys	GIG Deu	330	Arg GIU P	ro Asn Lys Gl ₃ 335	Val Asn Pro 340	
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att gat cgc atg atc aag gat gct gaa gct cac gct gat gag gac aag 1603 Ile Asp Arg Met Ile Lys Asp Ala Glu Ala His Ala Asp Glu Asp Lys 490 aag cgc cgc gag gag cag gaa gtc cgc aac aac gct gag tcc ctg gtt Lys Arg Arg Glu Glu Glu Glu Val Arg Asn Asn Ala Glu Ser Leu Val 505 tac cag acc cgc aag ttc gtt gaa gag aac tcc gag aag gtc tcc gaa 1699 Tyr Gln Thr Arg Lys Phe Val Glu Glu Glu Asn Ser Glu Lys Val Ser Glu 520 gac ctc aag gca aag gtc gaa gag gca gcc aag ggc gtt gaa gaa gca 1747 Asp Leu Lys Ala Lys Val Glu Glu Ala Ala Lys Gly Val Glu Glu Glu Ala	455	ry ite va.	460	nr Ala Lys	Asp Lys Gly 1 465	Thr Gly Lys	1507
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535 And Mys var Giu Giu Ala Ala Lys Gly Val Glu Ala	520)	52	d Glu Asn 5	Ser Glu Lys Va 530	al Ser Glu	1699
		gca aag Ala Lys	Agt GIG GIG	g gca gcc (1 Ala Ala)	Lys Gly Val Gl	a gaa gca u Glu Ala	1747

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gga Gly																163
ggc (211

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	t o Se	cc	gto Val	. Vá	t g	ca i	ttc Phe	gca Ala	Lys	eA e	n G	gt g Ly G	yaa Slu	gtt Val	ct Le	u Va	c g al G 50	gc ly	Glr	tcc Ser	259	
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PCT/IB00/00922

WO 01/00804

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z .

400

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Ala Val Glu Lys Leu Asn Thr Glu Ser Gln Glu Met Gly Lys Xaa Ile 565 570 575

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Glu Gly Ala Ala Asp Asp Asn Val Val Asp Ala Glu Val Val Glu Asp 595 600 605

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<210> 35

<211> 1947

<212> DNA

<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (101)..(1924)

<223> RXN02280

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cgt gat aat ttc caa gtt gac ctc ggc ggc gtt	gtt gat ctt ttg agt 163
Arg Asp Asn Phe Gln Val Asp Leu Gly Gly Val	Val Asp Leu Leu Ser
10 15	20
cgc cac att tat tcc ggt ccg agg gtg tat gtg	cgt gag ttg ctg cag 211
Arg His Ile Tyr Ser Gly Pro Arg Val Tyr Val	Arg Glu Leu Leu Gln
25 30	35
aat gcg gtt gat gct tgt act gca cgt tct gaa	cag ggt gag gag ggc 259
Asn Ala Val Asp Ala Cys Thr Ala Arg Ser Glu	Gln Gly Glu Glu Gly
40 45	50
tac gag ccg agt att cgt att cgg ccg gtg acc Tyr Glu Pro Ser Ile Arg Ile Arg Pro Val Thr 55 60	Lys Asp Arg Ala Thr 65
ttt tca ctg gtt gat aat ggt acg ggc ctg acc Phe Ser Leu Val Asp Asn Gly Thr Gly Leu Thr 70 75 80	Ala Gln Glu Ala Arg 85
gaa ttg ctg gcg acg gtg ggg cgg acg tcg aaa Glu Leu Leu Ala Thr Val Gly Arg Thr Ser Lys 90 95	Arg Asp Glu Phe Gly 100
ctg cag cgg gaa ggt cgc ctg ggg caa ttt ggc	atc ggg ctg ctt agt 451
Leu Gln Arg Glu Gly Arg Leu Gly Gln Phe Gly	Ile Gly Leu Leu Ser
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tgt ttc atg gtg gcg gat gag atc acc atg gtg (Cys Phe Met Val Ala Asp Glu Ile Thr Met Val S 120	Ser His Ala Glu Gly 130
	Gly Thr Phe Asn Leu 145
gag att ctt ggg gat gac gca acg gat gtc att c	ccg gtg ggc acg act 595
Glu Ile Leu Gly Asp Asp Ala Thr Asp Val Ile P	Pro Val Gly Thr Thr
150 155 160	165
gtg cac ctg act ccg cgc cct gat gag cgc acg t	tg ctg acg gaa aat 643
Val His Leu Thr Pro Arg Pro Asp Glu Arg Thr L	eu Leu Thr Glu Asn
170 175	180
tcc gtg gtc acc att gct agt aat tat ggc cgc to	ac ctg ccg att cct 691
Ser Val Val Thr Ile Ala Ser Asn Tyr Gly Arg Ty	yr Leu Pro Ile Pro
185	195
att gtg gtg cag ggt gag aaa aac acc acc atc ac	or aca tog cog gtg 739
Ile Val Val Gln Gly Glu Lys Asn Thr Thr Ile Th	or Thr Ser Pro Val
200 205	210

								\								4		r C I/IBC
t t Ph	e A	ca a la 1 15	aag Lys	gat Asp	act	t ga r As _i	t ca p G1 22	n Gl	ng c	ac a	agg Arg	ctg Leu	Ty:	: Ala	gg Gl	у Ал	g ga g Gl	g 787 u
Ar 23	g Le	eu (ìГÀ	Lys	Thi	235	o Pho	e As	p Vá	al 1	lle	Asp 240	Leu	Thr	Gl	y Pr	t gg o G1: 24:	y 5
.II	e GJ	Lu G	gTÀ	Val	A1a 250	Туг	Va.	l Le	u Pr	o 0 2	:1u :55	Ala	Gln	Ala	Pr	o Hi 26	•	=
Sei	r Ar	g A	rg	H1S 265	Ser	Ile	Туг	· Val	1 As 27	n A	rg	Met	Leu	Val	Se: 275	r As	t ggg p Gly	,
Pro	Se	r T 2	hr \ 80	Val	Leu	Pro	Asn	285	Al 5	a P	he	Phe	Val	Glu 290	Суз	Gl:	a ato u Ile	•
Asn	29	r T	hr A	<i>l</i> sp	Leu	Glu	Pro 300	Thr	: Al	a So	er i	Arg	Glu 305	Ala	Leu	Me1	g gat E Asp	
Asp 310	Th:	r Al	la F	he'	Ala	Ala 315	Thr	Arg	Glu	ı Hi	is :	11e 320	Gly	Glu	Cys	Ile	aaa Lys 325	1075
Ser	Tr	o re	u 1	ıe.	330	Leu	Ala	Met	Thr	: Ly 33	rs E 85	Pro	His	Arg	Val	Arg 340		1123
Pne	Thr	. AI	a I. 3	1e 1 45	His	Asp	Leu	Ala	150	Ar	g G	lu :	Leu	Cys	Gln 355	Ser	gac Asp	1171
Ala	Asp	36	u A.	la (Glu '	Thr	Met	Leu 365	Gly	Le	u L	eu 1	Chr	Leu 370	Glu	Thr	tcc Ser	1219
AIG	375	Ar	3 II	le s	er .	rie (380 31A	Glu	Ile	Th	r T	hr I	leu : 885	Ser	Ile	Thr	gag Glu	1267
gat Asp 390	vaı	Sei	. Le	eu G	3 Tu I	.ец <i>1</i> 195	Ala '	Thr	Thr	Leu	1 As 4(sp A	g de	Phe A	Arg	Gln	Leu 405	1315
aac Asn	Inr	116	: AI	а А. 4.	rg P 10	ro A	sp 1	[hr]	Leu	Ile 415	: Il	le A	sn G	ly (ly	Tyr 420	Ile	1363
cac (gac Asp	Ser	As ₁	b re	tgg euA	ct c la A	gg c rg I	eu]	lle 130	ccc Pro	gt Va	t c	ac t is T	yr P	ro 35	ccg Pro	ctt Leu	1411

PCT/IB00/00922

. WO 01/00804

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Thr	Val	Ser 440	Thi	r Ala	a As _i	p Leu	Arg 445		u Sei	r Met	t Asp	Leu 450		GIL	Leu	
ccg Pro	ecg Pro 455	Leu	Glr	g gad n Asp	ati Ile	t gag e Glu 460	Lys	gco Ala	c aaq a Lys	g gca s Ala	a ctg Leu 465	Asp	gcg	g cag Gln	gtc Val	1507
acg Thr 470	gaa Glu	tca Ser	ttg Lev	j aag Lys	gat Asp 475	ttt Phe	cag Gln	ato Ile	c aag e Lys	g ggc Gly 480	/ Ala	acg Thr	agg Arg	gtt Val	ttt Phe 485	1555
gaa Glu	ccc Pro	gca Ala	gat Asp	gtt Val 490	Pro	gcc Ala	gtg Val	gtg Val	atc 11e 495	Ile	gat Asp	tcc Ser	aag Lys	gcg Ala 500	cag Gln	1603
gcc Ala	tca Ser	cgg Arg	gat Asp 505	cgc Arg	aat Asn	gaa Glu	aca Thr	caa Gln 510	Ser	gca Ala	acc Thr	act Thr	gat Asp 515	cgt Arg	tgg Trp	1651
gct Ala	gac Asp	att Ile 520	ttg Leu	gca Ala	acg Thr	gtg Val	gat Asp 525	aac Asn	acg Thr	ttg Leu	agc Ser	cgt Arg 530	caa Gln	aca Thr	gcc Ala	1699
Asn	att Ile 535	cca Pro	cag Gln	gat Asp	cag Gln	gga Gly 540	ctg Leu	tcg Ser	gcg Ala	ttg Leu	tgc Cys 545	ttg Leu	aat Asn	tgg Trp	aac Asn	1747
aat Asn 550	tcg Ser	ctg Leu	gtc Val	agg Arg	aaa Lys 555	ttg Leu	gcg Ala	tcc Ser	act Thr	gat Asp 560	gac Asp	acc Thr	gcc Ala	gtg Val	gtg Val 565	1795
tcg Ser	cgc Arg	acg Thr	gtg Val	cgt Arg 570	ttg Leu	ctc Leu	tac Tyr	gtt Val	cag Gln 575	gca Ala	ttg Leu	ttg Leu	tcc Ser	agc Ser 580	aag Lys	1843
agg (Arg	cca Pro	Leu	cgg Arg 585	gtg Val	aag Lys	gaa Glu	Arg .	gcg Ala 590	ctg Leu	ctt Leu	aat Asn	Asp	tcg Ser 595	ctg Leu	gca Ala	1891
gat d Asp I	Leu '	gtt Val 600	tct Ser	ttg Leu	tct Ser	Leu :	tca Ser :	tcc Ser	gat Asp	atc Ile	taag	acaa	tc c	tccg	čtaat	1944
ctt					•				•	٠						1947
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Val A	sp L	eu L	eu S 20	er A	rg H	lis I		yr S 25	Ser G	Sly H	Pro A	rg V	al :	Tyr V	/al	

- Arg Glu Leu Leu Gln Asn Ala Val Asp Ala Cys Thr Ala Arg Ser Glu
 35 40 _ 45
- Gln Gly Glu Glu Gly Tyr Glu Pro Ser Ile Arg Ile Arg Pro Val Thr
 50 55 60
- Lys Asp Arg Ala Thr Phe Ser Leu Val Asp Asn Gly Thr Gly Leu Thr 65 70 75 80
- Ala Gln Glu Ala Arg Glu Leu Leu Ala Thr Val Gly Arg Thr Ser Lys 85 90 95
- Arg Asp Glu Phe Gly Leu Gln Arg Glu Gly Arg Leu Gly Gln Phe Gly 100 105 110
- Ile Gly Leu Leu Ser Cys Phe Met Val Ala Asp Glu Ile Thr Met Val 115 120 125
- Ser His Ala Glu Gly Ala Ser Ala Ile Arg Trp Thr Gly His Ala Asp 130 135 140
- Gly Thr Phe Asn Leu Glu Ile Leu Gly Asp Asp Ala Thr Asp Val Ile 145 150 155 160
- Pro Val Gly Thr Thr Val His Leu Thr Pro Arg Pro Asp Glu Arg Thr 165 170 175
- Leu Leu Thr Glu Asn Ser Val Val Thr Ile Ala Ser Asn Tyr Gly Arg 180 185 190
- Tyr Leu Pro Ile Pro Ile Val Val Gln Gly Glu Lys Asn Thr Thr Ile 195 200 205
- Thr Thr Ser Pro Val Phe Ala Lys Asp Thr Asp Gln Gln His Arg Leu 210 215 220
- Tyr Ala Gly Arg Glu Arg Leu Gly Lys Thr Pro Phe Asp Val Ile Asp 225 230 235 240
- Leu Thr Gly Pro Gly Ile Glu Gly Val Ala Tyr Val Leu Pro Glu Ala 245 250 255
- Gln Ala Pro His Met Ser Arg Arg His Ser Ile Tyr Val Asn Arg Met 260 265 270
- Leu Val Ser Asp Gly Pro Ser Thr Val Leu Pro Asn Trp Ala Phe Phe 275 280 285
- Val Glu Cys Glu Ile Asn Ser Thr Asp Leu Glu Pro Thr Ala Ser Arg 290 295 300
- Glu Ala Leu Met Asp Asp Thr Ala Phe Ala Ala Thr Arg Glu His Ile 305 310 315 320
- Gly Glu Cys Ile Lys Ser Trp Leu Ile Asn Leu Ala Met Thr Lys Pro 325 330 335



- His Arg Val Arg Glu Phe Thr Ala Ile His Asp Leu Ala Leu Arg Glu 340 345 350
- Leu Cys Gln Ser Asp Ala Asp Leu Ala Glu Thr Met Leu Gly Leu Leu 355 360 365
- Thr Leu Glu Thr Ser Arg Gly Arg Ile Ser Ile Gly Glu Ile Thr Thr 370 375 380
- Leu Ser Ile Thr Glu Asp Val Ser Leu Gln Leu Ala Thr Thr Leu Asp 385 390 395 400
- Asp Phe Arg Gln Leu Asn Thr Ile Ala Arg Pro Asp Thr Leu Ile Ile 405 410 415
- Asn Gly Gly Tyr Ile His Asp Ser Asp Leu Ala Arg Leu Ile Pro Val 420 425 430
- His Tyr Pro Pro Leu Thr Val Ser Thr Ala Asp Leu Arg Glu Ser Met 435 440 445
- Asp Leu Met Glu Leu Pro Pro Leu Gln Asp Ile Glu Lys Ala Lys Ala 450 455 460
- Leu Asp Ala Gln Val Thr Glu Ser Leu Lys Asp Phe Gln Ile Lys Gly 465 470 475 480
- Ala Thr Arg Val Phe Glu Pro Ala Asp Val Pro Ala Val Val Ile Ile
 485 490 495
- Asp Ser Lys Ala Gln Ala Ser Arg Asp Arg Asn Glu Thr Gln Ser Ala
 500 505 510
- Thr Thr Asp Arg Trp Ala Asp Ile Leu Ala Thr Val Asp Asn Thr Leu 515 520 525
- Ser Arg Gln Thr Ala Asn Ile Pro Gln Asp Gln Gly Leu Ser Ala Leu 530 540
- Cys Leu Asn Trp Asn Asn Ser Leu Val Arg Lys Leu Ala Ser Thr Asp 545 550 555 560
- Asp Thr Ala Val Val Ser Arg Thr Val Arg Leu Leu Tyr Val Gln Ala 565 570 575
- Leu Leu Ser Ser Lys Arg Pro Leu Arg Val Lys Glu Arg Ala Leu Leu 580 585 590
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cgt gat aat ttc caa gtt gac ctc ggc ggc gtt gtt gat ctt ttg agt Arg Asp Asn Phe Gln Val Asp Leu Gly Gly Val Val Asp Leu Leu Ser 10 15 20	163
cgc cac att tat tcc ggt ccg agg gtg tat gtg cgt gag ttg ctg cag Arg His Ile Tyr Ser Gly Pro Arg Val Tyr Val Arg Glu Leu Leu Gln 25 30 35	211
aat gcg gtt gat gct tgt act gca cgt tct gaa cag ggt gag ggc Asn Ala Val Asp Ala Cys Thr Ala Arg Ser Glu Gln Gly Glu Glu Gly 40 45 50	259
tac gag ccg agt att cgt att cgg ccg gtg acc aag gat cgt gcc acg Tyr Glu Pro Ser Ile Arg Ile Arg Pro Val Thr Lys Asp Arg Ala Thr 55 60 65	307
ttt tca ctg gtt gat aat ggt acg ggc ctg acc gcg cag gag gcg cgg Phe Ser Leu Val Asp Asn Gly Thr Gly Leu Thr Ala Gln Glu Ala Arg 70 75 80 85	355
gaa ttg ctg gcg acg gtg ggg cgg acg tcg aaa cgc gat gaa ttc ggt Glu Leu Leu Ala Thr Val Gly Arg Thr Ser Lys Arg Asp Glu Phe Gly 90 95 100	403
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Val Asp Leu Leu Ser Arg His Ile Tyr Ser Gly Pro Arg Val Tyr Val 20 25 30	

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Arg Glu Leu Leu Gln Asn Ara Val Asp Ala Cys Thr Ala Arg Ser Glu
35 40 45

Gln Gly Glu Glu Gly Tyr Glu Pro Ser Ile Arg Ile Arg Pro Val Thr 50 60

Lys Asp Arg Ala Thr Phe Ser Leu Val Asp Asn Gly Thr Gly Leu Thr 65 70 75 80

Ala Gln Glu Ala Arg Glu Leu Leu Ala Thr Val Gly Arg Thr Ser Lys
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Arg Asp Glu Phe Gly Leu Gln Arg Glu Gly Arg Leu Gly Gln Phe Gly 100 105 110

<210> 39

<211> 1269

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<223> RXA00886

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- tgattaatct gtttagaagc taaaggaagt atcacccacc gtg gca cgt gac tat 115
 Val Ala Arg Asp Tyr
 1 5
- tac ggc att ctc ggc gtc gat cgc aat gca acc gaa tca gag atc aaa 163
 Tyr Gly Ile Leu Gly Vad Asp Arg Asn Ala Thr Glu Ser Glu Ile Lys
 10 15 20
- aag gca tac cga aag ctt gcc cgc aaa tac cac ccg gac gta aac cca 211 Lys Ala Tyr Arg Lys Leu Ala Arg Lys Tyr His Pro Asp Val Asn Pro 25 30 35
- ggt gag gaa gca gcg gag aaa ttc cgc gag gct tct gtt gcg cat gag 259 Gly Glu Glu Ala Ala Glu Lys Phe Arg Glu Ala Ser Val Ala His Glu 40 45 50
- gta ctc act gat ccg gat aag cgc cgc att gtt gat atg ggc ggt gac 307 Val Leu Thr Asp Pro Asp Lys Arg Arg Ile Val Asp Met Gly Gly Asp 55 60 65
- cca atg gag caa ggc ggc gga gct ggc gct ggt ggc ttc ggt gga ggc 355
 Pro Met Glu Gln Gly Gly Gly Ala Gly Ala Gly Gly Phe Gly Gly Gly
 70 80 85

ttc ggc ggc agc ggt gga ctg ggc gat atc ttc gat gcc ttc ttc ggc 403

Phe	Gly	Gly	/ Ser	Gly 90	Gly	Leu	Gly	Asp	Ile 95	Phe	Asp	Ala	Phe	Phe 100	Gly	
G] y	ggc Gly	gcg Ala	ggc Gly 105	ggt	tcc Ser	cgt Arg	gga Gly	cca Pro 110	Arg	tcc Ser	cgc Arg	gtg Val	cag Gln 115	cca Pro	ggc Gly	451
agt Ser	gac Asp	acc Thr 120	ttg Leu	tgg Trp	cgc Arg	acc Thr	tcc Ser 125	atc Ile	acc Thr	ttg Leu	gaa Glu	gag Glu 130	gct Ala	tac Tyr	aag Lys	499
ggc Gly	gct Ala 135	aag Lys	aaa Lys	gat Asp	Leu !	hr 140	ctt Leu	gac Asp	acc Thr	gca Ala	gtg Val 145	ctg Leu	tgt Cys	acc Thr	aag Lys	547
tgt Cys 150	cat His	ggt Gly	tct Ser	gga Gly	tct o Ser <i>F</i> 155	jca la	tcc Ser	gac Asp	aag Lys	aag Lys 160	cct Pro	gtt Val	acc Thr	tgt Cys	ggc Gly 165	595
acc Thr	tgt Cys	aat Asn	ggc Gly	gct (Ala (170	ggt g Gly G	aa a lu :	att Ile	cag Gln	gaa Glu 175	gtg Val	cag (Gln i	cgc a	Ser	ttc Phe 180	ctg Leu	643
ggc (aac Asn	vaı	atg Met 185	acg t Thr S	cc c Ser A	gc o	ro (tgc Cys 190	cac His	acc f	tgc (Cys <i>l</i>	Asp (gc a Sly 1	acc Thr	ggt Gly	691
gag a Glu 1	Lie .	atc Ile 200	cca (Pro 1	gat c Asp P	ro C	ys T	ct o hr 0	gag · Glu (tgt (Cys i	gca q Ala <i>H</i>	Ma A	at g sp G	gt d ly #	gt (Arg '	gtg Val	739
cgt g Arg A	ct o la <i>l</i> 15	ege (Arg)	ege q Arg <i>P</i>	gac a Asp I	tc gt le Va 22	II A	cc a la A	ac a Asn]	atc ([le]	Pro A	ct g la G 25	gc a ly I	tc c le G	ag t	cc Ser	787
ggc a Gly M 230	tg d let A	gc a	itc c	rg we	tg go et Al 85	a go	gc c ly G	aa g ln G	Sly G	ag g lu V 40	tt g al G	gc g ly A	ct g la G	ly G	gc 1y 45	835
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atc to	tc a he T	III A	gc ga rg A: 65	at gg sp Gl	c gad y Ası	c ga p As	P Le	tg c eu H 70	ac g is A	cc aq la Se	gc at er Il	c aa le Ly 27	s Va	tt c	ca ro	931
atg tt Met Ph	ie v	at ge sp Al 30	ca go la Al	eg ct la Le	t ggd u Gly	e ac 7 Th 28	r G1	a ti lu Le	tg ga eu As	ac gt sp Va	g ga 1 G1 29	u Se	c ct r Le	c ac	ec nr	979
ggc ga Gly Gl 29	.u G1	ig gt .u Va	g aa l Ly	a ati	t acc Thr 300	TT	c cc e Pr	t go o Al	a go .a Gl	yt ac y Th 30	r Gl	g cc n Pr	c aa o As	c ga n As	it ip	1027
gtg at Val Il	c ac e Th	c tt	g ga u As	t ggt p Gly	gaa Glu	gg(at Me	g cc t Pr	g aa o Ly	g ct	g cg u Ar	c gc. g Ala	a ga a Gl	a gg u Gl	À C	1075

315

320

cac ggc aac ctc atg gcg cat gtc gat cta ttt gtg cca acc gat ttg. His Gly Asn Leu Met Ala His Val Asp Leu Phe Val Pro Thr Asp Leu 330 335

gat gac ege ace ege gaa ttg ett gaa gaa ate ege aac eat ege age 1171 Asp Asp Arg Thr Arg Glu Leu Leu Glu Glu Ile Arg Asn His Arg Ser 350

gac aac gct tcc gtg cat cgc gaa ggc gga gaa gaa tcc ggt ttc ttt 1219 Asp Asn Ala Ser Val His Arg Glu Gly Gly Glu Glu Ser Gly Phe Phe 360 365

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Ser Val Ala His Glu Val Leu Thr Asp Pro Asp Lys Arg Arg Ile Val

Asp Met Gly Gly Asp Pro Met Glu Gln Gly Gly Gly Ala Gly Ala Gly

Gly Phe Gly Gly Gly Phe Gly Gly Ser Gly Gly Leu Gly Asp Ile Phe

Asp Ala Phe Phe Gly Gly Gly Ala Gly Gly Ser Arg Gly Pro Arg Ser

Arg Val Gln Pro Gly Ser Asp Thr Leu Trp Arg Thr Ser Ile Thr Leu 115 120

Glu Glu Ala Tyr Lys Gly Ala Lys Lys Asp Leu Thr Leu Asp Thr Ala

Val Leu Cys Thr Lys Cys His Gly Ser Gly Ser Ala Ser Asp Lys Lys 145 150 155 160 Pro Val Thr Cys Gly Thr Cys Asn Gly Ala Gly Glu Ile Gln Glu Val 165 170 175

Gln Arg Ser Phe Leu Gly Asn Val Met Thr Ser Arg Pro Cys His Thr 180 185 190

Cys Asp Gly Thr Gly Glu Ile Ile Pro Asp Pro Cys Thr Glu Cys Ala 195 200 205

Ala Asp Gly Arg Val Arg Ala Arg Arg Asp Ile Val Ala Asn Ile Pro 210 215 220

Ala Gly Ile Gln Ser Gly Met Arg Ile Arg Met Ala Gly Gln Gly Glu 225 235 240

Val Gly Ala Gly Gly Pro Ala Gly Asp Leu Tyr Ile Glu Val Met 245 250 255

Val Arg Pro His Ala Ile Phe Thr Arg Asp Gly Asp Asp Leu His Ala 260 265 270

Ser Ile Lys Val Pro Met Phe Asp Ala Ala Leu Gly Thr Glu Leu Asp 275 280 285

Val Glu Ser Leu Thr Gly Glu Glu Val Lys Ile Thr Ile Pro Ala Gly 290 295 300

Thr Gln Pro Asn Asp Val Ile Thr Leu Asp Gly Glu Gly Met Pro Lys 305 310 315 320

Leu Arg Ala Glu Gly His Gly Asn Leu Met Ala His Val Asp Leu Phe 325 330 335

Val Pro Thr Asp Leu Asp Asp Arg Thr Arg Glu Leu Leu Glu Glu Ile 340 345 350

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<210> 41

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<223> RXS00568

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Val Lys Ser Ser Val

																L				Э	
	ga G1	aga Lu I	ag ys	Ct:	g ad u Se	gc g er A	sp 1	cc hr	egt Arg	tca Ser	aa Ly	s I	tc le 15	acc Thr	gtt Val	ga Gli	g gt u Va	11 P	ca ro 20	ttt Phe	163
	t c Se	t g er G	aa lu	Lei	3 T/2	ag c /s P 25	ca ç ro G	ag a	itc (le	gac Asp	G1:	n A	ca la '	tac Tyr	gcc	gct Ala	a Le	a go u Al	eg La	cag Gln	211
	ca Gl	ag nV	tc al	Glr 40	1 11	.c c .e P	ct g ro G	gt t ly E	tc he	cgt Arg 45	aac Ly:	g gg	gc a Ly I	aag Lys	gca Ala	ecç Pro) Ar	t ca g Gl	ig .n	ctt Leu	259
	at Il	e A	sp 55	gca Ala	cg Ar	c ti g Pi	tc g ne G	gc c ly A	gt rg 60	ggt Gly	gcg	g gt a Va	t d	tg Leu	gag Glu 65	cag Gln	gt: Va	t gt l Va	.c 1	aac Asn	307
	gad Ası 70) ME	g	ctt Leu	Pr	t aa o As	n A	gc t cg T 75	ac o yr 1	gca Ala	Gln	g gc Al	a I	tc le 80	gaa Glu	gct Ala	gaq Gli	g gg ı Gl	с ; у :	atc Ile 85	355
	aaq Lys	g gc s Al	a i	atc Ile	gg(Gl _y	A GT	g co n Pr O	t a	ac g sn V	gta /al	gag Glu	gt Va 9	1 T	cc . hr :	aag Lys	atc Ile	gaa Glu	a ga a As; 10	p <i>1</i>	aac Asn	403
	gag Glu	ct Le	c q u l	gtt /al	gaç Glu 105	ı Ph	c gt e Va	c go l Al	a G	lu	gtt Val 110	ga As _l	c g o Va	tt d	egc Arg	cca Pro	gag Glu 115	Phe	e G	gag Slu	451
	ctt Leu	Pr	0 1	ag ys .20	ttc Phe	gaq Glu	g ga u As	c at p Il	e T	ct d hr 1 25	gtt Val	gaç Glu	ggt 1Va	al F	ro .	gct Ala 130	atc Ile	aaq Lys	J 9	ct	499
	gac Asp	gaa Glu 135	ı G	ag lu	gca Ala	ato Ile	ga Gl	a gc ı Al 14	a G	ag d lu I	ctc Leu	gaç Glu	ac Th	r L	tg d eu 1 45	cgt Arg	gca Ala	cgt Arg	t P	tc he	547
	tcc Ser 150	acc Thr	C L	tg :	aag Lys	gat Asp	His 155	As	c ca	ac a is I	ag .ys	ctg Leu	aa Ly 16	s L	ag g ys G	ggt Sly (gag Glu	ttc Phe	Va	tc al 65	595
	acc Thr	atc	: aa : As	ac a	atc Ile	acc Thr 170	gca Ala	ago Sei	at Il	t g .e A	sp	ggt Gly 175	ga Gl	g aa u Ly	ag a y s I	itt d	gaa Glu	gag Glu 180	go Al	ca la	643
	acc Thr	act Thr	ga G1	Lu	ggt 31y 185	ctg Leu	tcc Ser	tac Tyr	ga Gl	u I	tc (le (gga Gly	tc: Se:	t ga c As	ac g Sp A	sp I	etg Leu .95	att Ile	ga As	ic ip	691
(ggc Gly	ctg Leu	ga As 20	P L	ag ys .	gct Ala	ctg Leu	atc Ile	gg G1 20	y A.	ct a la I	aag Lys	aaq Lys	g ga B As	p G.	aa a lu T 10	hr	gta Val	ga Gl	g u	739
İ	tc a	acc Ihr	tc Se	t g r G	ag (ctg Leu	gca Ala	aac Asn	gg(c ga y Gl	ig c	ac	aag Lys	gg Gl	c aa y Ly	ag g ys G	aa q lu <i>l</i>	gct Ala	ca Gl:	a n	787



225

atc age gtt gag atc acc gca acc aag cag cgc gag ctg cct gag ctg Ile Ser Val Glu Ile Thr Ala Thr Lys Gln Arg Glu Leu Pro Glu Leu 230 235 240 245	l
gat gat gag ttc gca cag ctg gct tct gag ttc gac acc atc gaa gag Asp Asp Glu Phe Ala Gln Leu Ala Ser Glu Phe Asp Thr Ile Glu Glu 250 255 260	
ctt cgt gag tcc acc gtg tct gac gtt gag gct aag cag aag aac gag Leu Arg Glu Ser Thr Val Ser Asp Val Glu Ala Lys Gln Lys Asn Glu 265 270 275	
cag gct gct gca atc cgc gac gaa gtt ctc gct gcg gct ctt ggc gag Gln Ala Ala Ile Arg Asp Glu Val Leu Ala Ala Ala Leu Gly Glu 280 285 290	979
gct gac ttc gct ctg cca cag tcc atc gtt gac gag cag gca cac tcc Ala Asp Phe Ala Leu Pro Gln Ser Ile Val Asp Glu Gln Ala His Ser 295 300 305	1027
cag ctg cac cag ctc ctc ggc gag ctt gca cac gac gat gct gca ctg Gln Leu His Gln Leu Leu Gly Glu Leu Ala His Asp Asp Ala Ala Leu 310 315 320 325	1075
aac tcc ctc ctt gag gct cag ggc acc act cgt gaa gag ttc gac aag Asn Ser Leu Leu Glu Ala Gln Gly Thr Thr Arg Glu Glu Phe Asp Lys 330 335 340	1123
aag aac gtc gaa gat gct gag aag gct gtt cgc acc cag ctg ttc ctg Lys Asn Val Glu Asp Ala Glu Lys Ala Val Arg Thr Gln Leu Phe Leu 345 350 355	1171
gac acc ctc tct gag gtt gag gag cct gag gtt tcc cag cag gag ctc Asp Thr Leu Ser Glu Val Glu Glu Pro Glu Val Ser Gln Gln Glu Leu 360 365 370	1219
acc gac cac atc ctg ttc acc gca cag tct tac ggc atg gac cca aac Thr Asp His Ile Leu Phe Thr Ala Gln Ser Tyr Gly Met Asp Pro Āsn 375 380 385	1267
cag ttc atc ggt cag ctg cag cag tcc ggc cag atc gcg aac ctc ttc Gln Phe Ile Gly Gln Leu Gln Gln Ser Gly Gln Ile Ala Asn Leu Phe 390 395 400 405	1315
tcc gac gtt cgc cgt ggc aag gct ctt gca cag gct atc tgc cgc gta Ser Asp Val Arg Arg Gly Lys Ala Leu Ala Gln Ala Ile Cys Arg Val 410 415 420	1363
aac gtg aag gac tcc gag ggt aac gag atc gac cct aag gaa tac ttc Asn Val Lys Asp Ser Glu Gly Asn Glu Ile Asp Pro Lys Glu Tyr Phe 425 430 435	1411
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1470

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Val Glu Val Pro Phe Ser Glu Leu Lys Pro Glu Ile Asp Gln Ala Tyr 20 25 30

Ala Ala Leu Ala Gln Gln Val Gln Ile Pro Gly Phe Arg Lys Gly Lys 35 40 45

Ala Pro Arg Gln Leu Ile Asp Ala Arg Phe Gly Arg Gly Ala Val Leu 50 60

Glu Gln Val Val Asn Asp Met Leu Pro Asn Arg Tyr Ala Gln Ala Ile
65 70 75 80

Glu Ala Glu Gly Ile Lys Ala Ile Gly Gln Pro Asn Val Glu Val Thr 85 90 95

Lys Ile Glu Asp Asn Glu Leu Val Glu Phe Val Ala Glu Val Asp Val 100 105 110

Arg Pro Glu Phe Glu Leu Pro Lys Phe Glu Asp Ile Thr Val Glu Val 115 120 125

Pro Ala Ile Lys Ala Asp Glu Glu Ala Ile Glu Ala Glu Leu Glu Thr 130 135 140

Leu Arg Ala Arg Phe Ser Thr Leu Lys Asp His Asn His Lys Leu Lys 145 150 155 160

Lys Gly Glu Phe Val Thr Ile Asn Ile Thr Ala Ser Ile Asp Gly Glu 165 170 175

Lys Ile Glu Glu Ala Thr Thr Glu Gly Leu Ser Tyr Glu Ile Gly Ser 180 185 190

Asp Asp Leu Ile Asp Gly Leu Asp Lys Ala Leu Ile Gly Ala Lys Lys 195 200 205

Asp Glu Thr Val Glu Phe Thr Ser Glu Leu Ala Asn Gly Glu His Lys 210 215 220

Gly Lys Glu Ala Gln Ile Ser Val Glu Ile Thr Ala Thr Lys Gln Arg 225 230 235 240

Glu Leu Pro Glu Leu Asp Asp Glu Phe Ala Gln Leu Ala Ser Glu Phe 245 250 255

							,			~			-	-		-
		WO (1/008	04)									I
Asp	Th	r Il	e Gl 26	u Gl 0	u Le	u Arq	g Gl	u Se: 26!	r Th	r Va	l Se	r As _l	P Val		ı Ala	
Lys	Gl:	n Ly 27	s As 5	n Gl	u Gl	n Ala	Al. 28	a Ala	a Il	e Arc	J Asp	Glu 285	ı Val	. Le	ı Ala	
Ala	Ala 290	a Le	u Gl	y Glu	ı Ala	295	Phe	e Ala	Le:	u Pro	Glr 300		Ile	val	. Asp	
Glu 305	Glr	n Ala	a Hi:	s Ser	Glr 310	Leu	His	s Gln	Le	1 Leu 315		Glu	Leu	Ala	His 320	
Asp	Asp	Ala	a Ala	1 Leu 325	Asn	Ser	Leu	Leu	G1 u	Ala	Gln	Gly	Thr	Thr 335		
Glu	Glu	Phe	340	Lys	Lys	Asn	Val	Glu 345	Asp	Ala	Glu	Lys	Ala 350	Val	Arg	
Thr	Gln	Leu 355	Phe	Leu	Asp	Thr	Leu 360	Ser	Glu	Val	Glu	Glu 365	Pro	Glu	Val	
Ser	Gln 370	Gln	Glu	Leu	Thr	Asp 375	His	Ile	Leu	Phe	Thr 380	Ala	Gln	Ser	Tyr	
Gly 385	Met	Asp	Pro	Asn	Gln 390	Phe	Ile	Gly	Gln	Leu 395	Gln	Gln	Ser	Gly	Gln 400	
Ile .	Ala	Asn	Leu	Phe 405	Ser	Asp	Val	Arg	Arg 410	Gly	Lys	Ala	Leu	Ala 415	Gln	
Ala :	Ile	Cys	Arg 420	Val	Asn	Val	Lys	Asp 425	Ser	Glu	Gly	Asn	Glu 430	Ile	Asp	

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														•		
ga: Gl:	g tt u Le	a ac u Th	a gt ir Va	al Ar	gt aa gg Ly 10	a gga s Gly	a att y Ile	tco Ser	cgc Arg 15	, Val	cto Leu	tcg Ser	gta Val	a gce l Ala 2	g gtt a Val O .	163
gc: Ala	t ag a Se	t to r Se	r Il	c gg e Gl 25	a tt y Ph	c gga	a act	gta Val	. Leu	aca Thr	ggc	acc Thr	gg(Gl ₃	/ Il	c gca e Ala	211
gca Ala	a gc	a Gl	a ga n As O	c tc p Se	t gc r Ala	a ttt a Phe	gac Asp 45	Tyr	ggt Gly	atg Met	gat Asp	cca Pro 50	Asr	ato Met	g aac t Asn	259
tac Tyr	aac Ası 5	n Pr	g at o Il	c ga e As	t gad p Asi	ato File 60	Lys	gat Asp	cgt Arg	ccc Pro	gaa Glu 65	gga Gly	ttg Leu	tco Ser	aat Asn	307
ctt Leu 70	Pro	tao Ty:	c tt r Ph	c gga e Gl	a agt y Ser 75	: Lys	ttg Leu	acc Thr	agc Ser	tgg Trp 80	ggc Gly	tca Ser	tca Ser	tat Tyr	gcc Ala 85	355
acc Thr	gcc Ala	tca Sei	a too	c ggd r Gly 90	/ Val	gtg Val	acc Thr	tcc Ser	gcg Ala 95	ctc Leu	ccg Pro	cag Gln	tac Tyr	acc Thr 100	Asp	403
ccg Pro	cgc Arg	tac Tyr	Pro 105) Leu	ggc Gly	aaa Lys	gac Asp	gac Asp 110	ctg Leu	ccc Pro	aag Lys	gca Ala	acc Thr 115	atc Ile	gac Asp	451
atg Met	gag Glu	cca Pro 120	Glu	gtt Val	ctt Leu	gcg Ala	cgc Arg 125	ctt Leu	gag Glu	cga Arg	ttc Phe	gtc Val 130	ggc Gly	gtt Val	gac Asp	499
ggt Gly	gat Asp 135	cgc Arg	ato	cgc Arg	caa Gln	atc Ile 140	aac Asn	gcg Ala	tac Tyr	tcg Ser	cca Pro 145	tca Ser	atg Met	gga Gly	cgc Arg	547
acc Thr 150	att Ile	cct Pro	cta Leu	gtc Val	tgg Trp 155	gtt Val	gtt Val	cca Pro	Glu	gac Asp 160	aac Asn '	acc Thr	gtg Val	cct Pro	ggc GIÿ 165	595
cca Pro	acg Thr	gtc Val	tac Tyr	gca Ala 170	ctc Leu	gga Gly	ggc (Gly A	gac Asp 175	ggt (Gly (gga (Gly (caa Gln (ggc Gly	ggc Gly 180	cag Gln	643
aac Asn	tgg Trp	gtc Val	acc Thr 185	cgc Arg	acc Thr	gac Asp	Leu (gag (Glu (190	gaa 1 Slu 1	tta a Leu 1	acc a Thr S	Ser A	gac Asp 195	aac Asn	aac Asn	691
atc Ile	Asn	ctc Leu 200	atc Ile	atg Met	ccg Pro	atg d Met 1	ctc o Leu 0 205	gga t Sly S	ct t Ser E	tt a Phe S	Ser E	tc t he 1 210	ac Tyr	tct Ser	gac Asp	739
Trp /	gca Ala 215	cgc Arg	gaa Glu	agc Ser	Gln :	tcc a Ser N 220	atg g Met G	gt t	gt g Lys A	la G	aa c iln G 25	ag t iln T	gg (gaa Glu	aca Thr	787

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<210> 44

<211> 242

<212> PRT

<213> Corynebacterium glutamicum

<400> 44

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Leu Ser Val Ala Val Ala Ser Ser Ile Gly Phe Gly Thr Val Leu Thr
20 25 30

Gly Thr Gly Ile Ala Ala Ala Gln Asp Ser Ala Phe Asp Tyr Gly Met
35 40 45

Asp Pro Asn Met Asn Tyr Asn Pro Ile Asp Asp Ile Lys Asp Arg Pro 50 55 60

Glu Gly Leu Ser Asn Leu Pro Tyr Phe Gly Ser Lys Leu Thr Ser Trp
65 70 75 80

Gly Ser Ser Tyr Ala Thr Ala Ser Ser Gly Val Val Thr Ser Ala Leu 85 90 95

Pro Gln Tyr Thr Asp Pro Arg Tyr Pro Leu Gly Lys Asp Asp Leu Pro 100 105 110

Lys Ala Thr Ile Asp Met Glu Pro Glu Val Leu Ala Arg Leu Glu Arg 115 120 125

Phe Val Gly Val Asp Gly Asp Arg Ile Arg Gln Ile Asn Ala Tyr Ser 130 135 140

Pro Ser Met Gly Arg Thr Ile Pro Leu Val Trp Val Val Pro Glu Asp 145 150 155 160

Asn Thr Val Pro Gly Pro Thr Val Tyr Ala Leu Gly Gly Gly Asp Gly 165 170 175

Gly Gln Gly Gln Asn Trp Val Thr Arg Thr Asp Leu Glu Glu Leu 180 185 190

Thr Ser Asp Asn Asn Ile Asn Leu Ile Met Pro Met Leu Gly Ser Phe
195 200 205

Ser Phe Tyr Ser Asp Trp Ala Arg Glu Ser Gln Ser Met Gly Cys Ala 210 215 220

Gln Gln Trp Glu Thr Leu Leu Met His Glu Leu Pro Glu Pro Leu Val 225 230 235 240

Ala Ala



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ct Le	g cc u Pr	c aa o Ly	's Al	a ac a Th	c at r Il	c ga e As	c at p Me	g ga t Gl 2	u Pr	a ga o Gl	a gc u Al	t ct a Le	t gc u Al -3	a Ar	c ctt g Leu	96
ga Gl	g cg u Ar	g Ph	c gt e Va 5	c gg l Gl	c gt y Va	t ga l As	c gg p Gl	y As	t cg p Ar	c at g Il	c cg e Ar	c caa g Gl: 4:	ı Il	c aad e Asi	c gcg n Ala	144
ta: Ty:	c tc r Se: 50	r Pr	a tc o Se	a ate	g gga t Gly	a cgo / Aro	g Thi	ati	t cc = Pr	t cta o Lei	a gto u Vai	l Trp	g gto Vai	c gto l Val	g cca L Pro	192
gaa Glu 65	ı Ası	c aa o Ası	c ace	c gto r Val	g cct Pro 70	Gl	c cca / Pro	acç Thi	g gto Val	tad L Tyr 75	: Ala	a cto a Leu	ggo Gly	ggc Gly	ggc Gly 80	240
gac Asp	ggt Gly	ggc Gly	caa / Glr	a ggo n Gly 85	Gly	caa Gln	aac Asn	tgg Trp	gto Val	. Thr	c cgc Arg	acc Thr	gac Asp	ctt Leu 95	gat	288
gag Glu	ttg Leu	Thr	s agt Ser 100	Glu	aac Asn	aac Asn	atc Ile	aac Asn 105	Leu	ato	atg Met	ccč Pro	atg Met 110	Leu	gga Gly	336
tct Ser	ttt Phe	agt Ser 115	Phe	tac	gct Ala	gac Asp	tgg Trp 120	gca Ala	ggc	gaa Glu	agc Ser	gaa Glu 125	tcc Ser	atg Met	ggt Gly	384
ggt Gly	gcg Ala 130	caa Gln	cag Gln	tgg Trp	gaa Glu	aca Thr 135	ttc Phe	ctc Leu	atg Met	cac His	gaa Glu 140	ctr Xaa	ccm Xaa	gag Glu	ccg Pro	432
cta Leu 145	gaa Glu	gcg Ala	gcc Ala	atc Ile	ggc Gly 150	gca Ala	gac Asp	ggg Gly	caa Gln	cgc Arg 155	agc Ser	atc Ile	gtc Val	ggc Gly	atg Met 160	480
tcc Ser	atg Met	tcc Ser	ggg Gly	gga Gly 165	tcr Xaa	gtg Val	ctg Leu	Asn	ttt Phe 170	gcg Ala	acg Thr	cat His	gac Asp	ccc Pro 175	aac Asn	528

			. (

ttt tay tcc Phe Xaa Ser	tck gtc ggc tca Xaa Val Gly Ser 180	ttt tct gga tgt Phe Ser Gly Cys 185	gcc gaa acc aac tcc 576 Ala Glu Thr Asn Ser 190
			cta caa cgg caa tgt 624 Leu Gln Arg Gln Cys 205

cgt gcc tgagcaaatc tttggtgaag tag 653 Arg Ala 210

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Glu Arg Phe Val Gly Val Asp Gly Asp Arg Ile Arg Gln Ile Asn Ala

Tyr Ser Pro Ser Met Gly Arg Thr Ile Pro Leu Val Trp Val Val Pro

Glu Asp Asn Thr Val Pro Gly Pro Thr Val Tyr Ala Leu Gly Gly Gly

Asp Gly Gly Gln Gly Gln Asn Trp Val Thr Arg Thr Asp Leu Asp

Glu Leu Thr Ser Glu Asn Asn Ile Asn Leu Ile Met Pro Met Leu Gly 105

Ser Phe Ser Phe Tyr Ala Asp Trp Ala Gly Glu Ser Glu Ser Met Gly

Gly Ala Gln Gln Trp Glu Thr Phe Leu Met His Glu Xaa Xaa Glu Pro 135

Leu Glu Ala Ala Ile Gly Ala Asp Gly Gln Arg Ser Ile Val Gly Met

Ser Met Ser Gly Gly Xaa Val Leu Asn Phe Ala Thr His Asp Pro Asn 170

Phe Xaa Ser Xaa Val Gly Ser Phe Ser Gly Cys Ala Glu Thr Asn Ser

Trp Met Xaa Arg Arg Trp His Arg Ser His Cys Leu Gln Arg Gln Cys

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205

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<223> RXN03040

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Met Ser Xaa Gly Asp

1 5

aac gca ccg att gat gag gat gcg ttc aaa aac cgc gtc ttg gtt ggg 163 Asn Ala Pro Ile Asp Glu Asp Ala Phe Lys Asn Arg Val Leu Val Gly 10 15 20

ttt gaa atc gaa gct atg tcc aac acc tgc acc cat aac ctc aag gct 211 Phe Glu Ile Glu Ala Met Ser Asn Thr Cys Thr His Asn Leu Lys Ala 25 30 35

gcg acc gat caa atg ggc atc gac aac atc aac tac gat ttc cga cca 259 Ala Thr Asp Gln Met Gly Ile Asp Asn Ile Asn Tyr Asp Phe Arg Pro 40 45 50

acc gga acc cac gcc tgg gat tac tgg aac gaa gcg ctc cac cgc ttc 307
Thr Gly Thr His Ala Trp Asp Tyr Trp Asn Glu Ala Leu His Arg Phe
55 60 65

ttc ccg ttg atg atg cag ggc ttc ggc ctc gac ggt ggt ccc atc ccg 355
Phe Pro Leu Met Met Gln Gly Phe Gly Leu Asp Gly Gly Pro Ile Pro
70 75 80 85

atc tat aac cct aac ggt gtg acc tcc agc gag tct tct ntc aga act 403
Ile Tyr Asn Pro Asn Gly Val Thr Ser Ser Glu Ser Ser Xaa Arg Thr
90 95 100

gtc ttc tgatgtgagc cttggcaccn gtg 432
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<211> 103

<212> PRT

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Arg Val Leu Val Gly Phe Glu Ile Glu Ala Met Ser Asn Thr Cys Thr

His Asn Leu Lys Ala Ala Thr Asp Gln Met Gly Ile Asp Asn Ile Asn

Tyr Asp Phe Arg Pro Thr Gly Thr His Ala Trp Asp Tyr Trp Asn Glu

Ala Leu His Arg Phe Phe Pro Leu Met Met Gln Gly Phe Gly Leu Asp

Gly Gly Pro Ile Pro Ile Tyr Asn Pro Asn Gly Val Thr Ser Ser Glu 90

Ser Ser Xaa Arg Thr Val Phe 100

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<211> 835

<212> DNA

<213> Corynebacterium glutamicum

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<222> (101)..(835)

<223> RXN03051

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- atc gag tta ccg gag ggg gta agc aag gag aaa gct gac cag cta gaa 163 Ile Glu Leu Pro Glu Gly Val Ser Lys Glu Lys Ala Asp Gln Leu Glu
- gtt gcg gaa gcg cga ctt aac gag ggt gca cga ctg atg gca acc acc 211 Val Ala Glu Ala Arg Leu Asn Glu Gly Ala Arg Leu Met Ala Thr Thr 25
- ggg tgt gag gtt atg tgg cca acg ggc ttc tca gtt tgt ggc cga att. 259 Gly Cys Glu Val Met Trp Pro Thr Gly Phe Ser Val Cys Gly Arg Ile 40
- ctt gac acc tat cgc cag gtt gga ggt cag ttg tca tgg ctt ggg cca 307 Leu Asp Thr Tyr Arg Gln Val Gly Gln Leu Ser Trp Leu Gly Pro 55

ccg aag tca aac gag ttg acc aat ccc gac ggt gtt ggc aaa aga agt

)									
Pro 70		s Ser	Asr	ı Glu	Leu 75		Asn	Pro	Asp	61 g 80		Gly	' Lys	Arg	Ser 85	
					Ala					Pro					-	403
gca Ala	gtg Val	acc	Leu 105	Asp	ggt Gly	ttg Leu	cga Arg	cag Gln 110	Trp	ggg Gly	acc Thr	ttg Leu	aac Asn 115	tgg Trp	gaa Glu	451
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cca Pro 150	ttg Leu	act Thr	ggc Gly	ggt Gly	gct Ala 155	gtg Val	tgg Trp	ggc Gly	gat Asp	att Ile 160	aaa Lys	cag Gln	cgc Arg	tac Tyr	gaa Glu 165	595
gaa Glu	ctt Leu	ggc Gly	ggc Gly	tcg Ser 170	aat Asn	cat His	gcc Ala	att Ile	ggc Gly 175	atc Ile	ccg Pro	atc Ile	act Thr	aat Asn 180	gag Glu	643
cta Leu	cct Pro	agc Ser	ggt Gly 185	act Thr	gag Glu	tat Tyr	ttt Phe	tac Tyr 190	aat Asn	aat Asn	ttc Phe	tcc Ser	aat Asn 195	gga Gly	aca Thr	691
					gat Asp											739
Gln	cgg Arg 215	gtg Val	tgg Trp	gat Asp	gcg Ala	ttg Leu 220	ggt Gly	cgg Arg	gag Glu	acg Thr	ggt Gly 225	cgt Arg	tta Leu	ggt Gly	ttt Phe	787
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<212> PRT

<213> Corynebacterium glutamicum

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Val Cys Gly Arg Ile Leu Asp Thr Tyr Arg Gln Val Gly Gln Leu 55 50

Ser Trp Leu Gly Pro Pro Lys Ser Asn Glu Leu Thr Asn Pro Asp Gly

Val Gly Lys Arg Ser Glu Phe Phe Gly Gly Ala Ile Tyr Trp His Pro

Asp Thr Gly Ala Tyr Ala Val Thr Leu Asp Gly Leu Arg Gln Trp Gly

Thr Leu Asn Trp Glu Ser Gly Pro Leu Gly Tyr Pro Thr Ser Gly Pro

Met Asp Thr Asn Tyr Pro Leu Thr Gln Arg Gln Thr Phe Gln Gly Gly 135

Asp Asn Tyr Tyr Asn Pro Leu Thr Gly Gly Ala Val Trp Gly Asp Ile

Lys Gln Arg Tyr Glu Glu Leu Gly Gly Ser Asn His Ala Ile Gly Ile 170

Pro Ile Thr Asn Glu Leu Pro Ser Gly Thr Glu Tyr Phe Tyr Asn Asn

Phe Ser Asn Gly Thr Ile Ser Trp Arg Asn Asp Arg Gln Thr Arg Phe 195

Met Tyr Leu Ala Thr Gln Arg Val Trp Asp Ala Leu Gly Arg Glu Thr

Gly Arg Leu Gly Phe Pro Glu Ala Asp Glu Thr Pro Glu Val Ser Gly 225 240

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<223> RXN03054

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a I	ag ys	gct Ala	gca Ala	gg Gl	y ve	c a 1 I 0	tt (gct Ala	gca Ala	gc Al	a c a I	tt eu 15	ctt Leu	gti Val	gca L Ala	a go	gt g Ly G	gt 1y 20	ata Ile	163
			V	2.	5	11 G.	Ly (31N	АІА	3e:	r G	In	Val	Val	aca Thr	: Pr 3	o G	lu	Asp	211
G.	aa (ln <i>i</i>	gat Asp	gcg Ala 40	tai Tyi	t gt . Va	t ca 1 G1	n G	ag In	ttc Phe 45	cac His	C C S H.	ac is	gaa Glu	ggg Gly	aat Asn 50	Th	c c r P	ca ro	cct Pro	259
gt Va	tg q	gta /al 55	gac Asp	ggç Gly	gte Val	g gg L Gl	у С	gc 1 1y 1	tac Tyr	act Thr	ga G	ag (caa Gln	gaa Glu 65	atc Ile	gc Al	c ga a Gi	ag lu	atc Ile	307
***	s G	ag lu .	gct Ala	atc	Arg	Ca Gli 75	n A.	cc c la G	aa Sln	gaa Glu	t c Se	er G	80	gca Ala	cct Pro	aat Asi	t ga n Gl	a Lu	gag Glu 85	355
ct Le	c a u I	tt (le 1	ecg Pro	ggt Gly	gag Glu 90	Me	y to : Tr	gg t p S	ca er	gat Asp	aa Ly 9	's V	tg al	gag Glu	ctg Leu	cca Pro	a gt Va 10	1	act Thr	403
	C 11.	JP I		105	nia	WIG	AS	р С	1 u /	110	GL	u I	le A	Ala	att Ile	Ala 115	G1	n (Sln	451
		1	20		o.i.i	1111	AI	12	25	.eu	Ala	э A.	la F	lla .	gcg Ala 130	Ala	Cy	s G	ln	499
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gga Gly	gtc (Val (Gly	att Ile 425	agg Arg	gtt Val	cca Pro	Lys]	att g [le 6 30	ggg t	tt a Phe I	ag g Lys A	Ala A	agg Arg i	atg Met	gat Asp	1411
tgc (Cys)	Asp 1	ctt Leu 140	cct Pro	gga Gly	act Thr	Val S	ca g Ser A 145	gat g Asp V	ta g al V	rtg g 'al G	ly T	at g yr G 50	ga (tgg I'rp	att Ile	1459

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tt Ph 47	e P	tc he	ggt Gly	aa As	it aq on Ai	cg As	at to sn Se 75	et gi	t gt al Va	g ca l Gl	na ac .n Th 48	ır As	t tt n Le	a ga u Gl	g ġc u Al	eg ggt La Gly 485	
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gci Ala	t ta a Ty	r	ctt Leu 520	Pr	g tg o Cy	t ac s Th	g at r Il	a ga e As 52	p Ar	t ag g Se	t ta r	acat	aagg	aat	ggaa	tag	1701
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Glu 65	Ile	e A	la (Glu	Ile	His 70	Glu	Ala	Ile	Arg	Gln 75	Ala	Gln	Glu	Ser	Gly 80	
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PCT/IB00/00922

WO 01/00804

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155

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Ala His Ala Val Asn Asn Tyr Ser Ala Gln Val Trp Glu Arg Asn Gly 200

Trp Glu Ser Gly Trp Met Gly Tyr Pro Thr Gly Gly Glu Val Pro Val *

Asn Gly Ser Asn Pro Ile Asp Gly Glu Leu Ser Gly Trp Val Gln Thr

Phe Gln Gly Gly Arg Val Tyr Arg Ser Pro Val Leu Asp Gly Phe Gln

Val Ala Ser Ile Asn Gly Leu Ile Leu Asp Lys Trp Leu Glu Leu Gly

Gly Pro Asp Ser Asp Leu Gly Phe Pro Ile Ala Asp Glu Ala Val Thr

Ala Asp Gly Val Gly Arg Phe Ser Val Phe Gln Asn Gly Val Val Tyr 295

Trp His Pro Gln His Gly Ala His Pro Ile Leu Gly Asn Ile Tyr Ser 315

Ile Trp Arg Glu Glu Gly Ala Glu Ser Gly Glu Phe Gly Tyr Pro Ile

Gly Asp Pro Glu Lys Tyr Thr Glu Asn Met Ala Asn Gln Val Phe Glu

Lys Gly Glu Leu Ala Ala Asn Leu Tyr Pro Asn Pro Leu Glu Ala Phe

Ile Glu Phe Leu Pro Phe Ala Asn Leu Glu Glu Ala Ile Glu Tyr Phe 370

Glu Asn Gly Leu Ser Asn Ser Arg Val Glu Ala Asn Ser Leu Asn Ala 395

Lys Lys Asp Ser Ile Gln Cys Gln Ser Gln Ser Ala Asn Ile His Val

Arg Thr Lys Ser Asp Gly Val Gly Ile Arg Val Pro Lys Ile Gly Phe

Lys Ala Arg Met Asp Cys Asp Leu Pro Gly Thr Val Ser Asp Val Val 435

Gly Tyr Gly Trp Ile Tyr Tyr Asp Tyr Trp Gly Arg Trp Ala Gln Ala

	u	O 01/	/00 2 04	l												D
	• • •	01,														P
	450					455					460)				
Ala 465		Ala	Gln	Gln	Phe 470	Phe	Gly	Asn	Arg	Asn 475	Ser	Val	Val	Gln	Thr 480	
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tgtt	atcg	cc c	ctgg	atga	g ta	gtga	ttta	gag	gagt				gac Asp			
													cgc Ara			

tcg ggt gct tcc act acc tct acc tct tct tat gag gct aag cag gta Ser Gly Ala Ser Thr Thr Ser Thr Ser Ser Tyr Glu Ala Lys Gln Val tct aca cag aag aag tca tcc ggt tcg gat tct aag cct ggc ggt Ser Thr Gln Lys Lys Ser Ser Gly Ser Asp Ser Lys Pro Gly Gly Gly gtt att tct ttt ctg cct gag gtt gtg gga gaa gtc cgt aag gtt att Val Ile Ser Phe Leu Pro Glu Val Val Gly Glu Val Arg Lys Val Ile tgg cct act gcg cgc cag atg gtc acg tac acc ctt gtc gtt ttg gga Trp Pro Thr Ala Arg Gln Met Val Thr Tyr Thr Leu Val Val Leu Gly ttc ttg att gtt ttg acc gct ttg gtg tct ggt gtg gat ttc cta gct Phe Leu Ile Val Leu Thr Ala Leu Val Ser Gly Val Asp Phe Leu Ala ggt ctt gga gtt gag aag att ctg act ccg taggtaggat gtgtaacatc

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Lys Pro Gly Gly Gly Val Ile Ser Phe Leu Pro Glu Val Val Gly Glu
50 60

Val Arg Lys Val Ile Trp Pro Thr Ala Arg Gln Met Val Thr Tyr Thr 65 70 75 80

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Met Thr Lys Asp Val

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Pr	t ga o Gl	u H	ac to is So	ca c er G	ag c ln L	tg g eu V	tc a	igc Ser 45	Ţyr	ct Le	g aa u As	ic aa in As	in Al	c a: a I:	tc le	aag Lys	gca Ala	259
Gli	n Gl	a ct u Le 5	g ti eu Pl	tc a ne T	cc c hr A	rg A	ac a sp I 60	ag ys	gac Asp	ta Ty:	c at r Il	e Va	c co l Ar 55	gc aa g As	ac sn	ggc Gly	gaa Glu	307
gti Val 70	l Me	g at t Il	c gt e Va	c gal A	sp G	gc to Ly Pi 75	tc a	cc	ggc	cgi Arq	t gt g Va 8	l Le	t gc u Al	a Gl	gc Ly	cgc Arg	cga Arg 85	355
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at II	c aa le Ly	a ct 's Le	c cg u Ar 26	g Gl	a cg u Ar	t gg g Gl	a cti y Lei	t gat 1 Ası 270	Pr	t tto o Phe	c ga e Gl	a gad u Asp	ga: Gl: , 27:	u Gl	a ago u Ser	931
			u Al					ı Let					Glı		a tgc g Cys	
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- Thr Asp Leu Val Tyr Lys Thr Gln Glu Ala Lys Phe Ala Ala Val Val 165 170 175
- Asp Asp Ile Ala Glu Arg Thr Glu Lys Gly Gln Pro Val Leu Val Gly 180 185 190
- Thr Val Ser Val Glu Arg Ser Glu Tyr Leu Ser Gln Leu Leu Thr Lys 195 200 205
- Arg Gly Ile Lys His Asn Val Leu Asn Ala Lys His His Glu Gln Glu 210 215 220
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- Thr Asn Met Ala Gly Arg Gly Thr Asp Ile Val Leu Gly Gly Asn Pro 245 250 255
- Glu Ile Leu Leu Asp Ile Lys Leu Arg Glu Arg Gly Leu Asp Pro Phe 260 265 270
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- Met Lys Gln Arg Cys Glu Glu Arg Gly Asp Lys Val Arg Glu Ala Gly 290 295 300
- Gly Leu Tyr Val Leu Gly Thr Glu Arg His Glu Ser Arg Arg Ile Asp 305 310 315
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- Arg Phe Tyr Leu Ser Met Arg Asp Leu Met Val Arg Phe Val Gly 340 345
- Pro Thr Met Glu Asn Met Met Asn Arg Leu Asn Val Pro Asp Asp Val 355 360 365
- Pro Ile Glu Ser Lys Thr Val Thr Asn Ser Ile Lys Gly Ala Gln Ala 370 380
- Gln Val Glu Asn Gln Asn Phe Glu Met Arg Lys Asn Val Leu Lys Tyr

400

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Glu Ile Leu Glu Ser Ala Asp Ile Ser Arg Tyr Ile Gln Asn Met Ile 420 425 430

Glu Glu Thr Val Ser Ala Tyr Val Asp Gly Ala Thr Ala Asn Gly Tyr 435 440 445

Val Glu Asp Trp Asp Leu Asp Lys Leu Trp Asn Ala Leu Glu Ala Leu 450 455 460

Tyr Asp Pro Ser Ile Asn Trp Thr Asp Leu Val Glu Gly Ser Glu Tyr 465 470 475 480

Gly Lys Pro Gly Glu Leu Ser Ala Glu Asp Leu Arg Thr Ala Leu Val 485 490 495

Asn Asp Ala His Ala Glu Tyr Ala Lys Leu Glu Glu Ala Val Ser Ala 500 505 510

Ile Gly Gly Glu Ala Gln Ile Arg Asn Ile Glu Arg Met Val Leu Met 515 520 525

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Leu Lys Glu Gly Ile Gly Leu Arg Ala Met Ala Gln Arg Asp Pro Leu 545 550 555 560

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Glu										Pro				ttg Leu		787

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gca Ala 230	Cys	gat Asp	cca Pro	a gc	t gt a Va 23	l Gly	ggd Gly	gto Y Val	g ta L Ty:	t gt r Va 24	l Le	t ga u As;	t cc	t gc	a cct a Pro 245	835
ttg Leu	ctc Leu	aac Asn	ggo Gly	gaa y Glu 250	u Th	c gat r Asp	gaç Glu	g gaa n Glu	a aat 1 Ast 255	n Gl	t gc y Al	g cg	c cta g Le	a acc u Th: 26	c ggt r Gly O	883
aat Asn	gag Glu	atc Ile	gat Asp 265	Thi	c aad	c cgt n Arg	ccc Pro	270	: Thi	ggt Gly	t gg y Gl	a tto y Pho	c aad e Asi 275	ı Ala	c cag a Gln	931
tcc Ser	ggc Gly	cag Gln 280	Met	gaa Glu	ato Ile	e Ser	ttt Phe 285	Ala	tto Phe	aaa Lys	a to	c ggd r Gly 290	/ Asp	ggç Gl	g gaa / Glu	979
gaa Glu	ggc Gly 295	tct Ser	gca Ala	act Thr	tgg Trp	tcc Ser 300	Ser	ctg Leu	acc	ago Ser	Caq Glr 305	ı Tyr	cto Lev	r cag Glr	g cag n Gln	1027
cag Gln 310	atc Ile	gcc Ala	atc Ile	acc Thr	ctg Leu 315	Asp	tct Ser	cag Gln	gtg Val	att Ile 320	Ser	gca Ala	ccc Pro	gtg Val	att Ile 325	1075
cag Gln	tca Ser	gca Ala	acc Thr	cct Pro 330	gtg Val	ggt Gly	tct Ser	gca Ala	aca Thr 335	tcc Ser	ato	acc Thr	ggt	gac Asp 340		1123
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ttg Leu	Pro	ctg Leu 360	agc Ser	ttc Phe	gca Ala	ggt Gly	gaa Glu 365	aac Asn	ggc Gly	gag Glu	cgc Arg	ggc Gly 370	gga Gly	act Thr	acc Thr	1219
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atc of Ile A	yca (Ala (ggc Gly	atc Ile	gtc Val	ggc Gly 395	atc Ile	gcg Ala	ctg Leu	gtc Val	gcc Ala 400	atc Ile	ttc Phe	gtg Val	ttc Phe	gcc Ala 405	1315
tac t Tyr 1	ac d Yr F	egc (Val	ttc Phe 410	gga Gly	ttc Phe	gtt Val	Ser	ctg Leu 415	ttc Phe	acc Thr	ctg Leu	ttt Phe	gcc Ala 420	gca Ala	1363
ggc g Gly V	tg t al I	eu i	gtc /al :	tac (Tyr (ggc Gly	ctt (Leu 1	Leu \	gta (Val 1 430	ctg Leu	ctg Leu	gga Gly	cgc Arg	tgg Trp 435	atc Ile	gga Gly	1411
tat t Tyr S	er L	ta g eu A 40	gac (Asp 1	ctt (Leu <i>l</i>	gct (Ala (Gly 1	atc q [le <i>l</i> [45	gcc (Ala (ggt Gly	ttg Leu	atc Ile	atc Ile 450	ggt Gly	atc Ile	ggt Gly	1459

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acc Thr	Thr 455	Ala	gac Asp	tco Ser	tto Phe	gtg Val 460	. Val	tto Phe	tat Tyr	gag Glu	g cgc Arg 465	Ile	aag Lys	gat	gag Glu	150 7
ato Ile 470	Arg	gaa Glu	gga Gly	aga Arg	tco Ser 475	Phe	aga Arg	tct Ser	gca Ala	gta Val 480	Pro	cgt Arg	gca Ala	tgg Trp	gaa Glu 485	
agc Ser	gcc Ala	aag Lys	cgc Arg	acc Thr 490	Ile	gtc Val	aca Thr	ggc Gly	aac Asn 495	Met	gtc Val	act Thr	ttg Leu	ctc Leu 500	ggc	1603
gct Ala	atc Ile	gtg Val	att Ile 505	tac Tyr	ttg Leu	ctc Leu	gcg Ala	gtc Val 510	ggc Gly	gaa Glu	gtc Val	aag Lys	ggc Gly 515	ttt Phe	gcc Ala	1651
ttc Phe	acc Thr	ctg Leu 520	ggt Gly	ctg Leu	acc Thr	acc Thr	gta Val 525	ttc Phe	gat Asp	ctc Leu	gtt Val	gtc Val 530	acc Thr	ttc Phe	ctg Leu	169 9
atc Ile	acg Thr 535	gca Ala	cca Pro	ctg Leu	gtt Val	atc Ile 540	ctg Leu	gca Ala	tca Ser	cgc Arg	aac Asn 545	cca Pro	ttc Phe	ttt Phe	gcc Ala	1747
aag Lys 550	tca Ser	tcg Ser	gtc Val	aac Asn	ggc Gly 555	atg Met	gga Gly	cga Arg	gtg Val	atg Met 560	aag Lys	ctc Leu	gtt Val	gaa Glu	gaa Glu 565	1795
cgc	cgc Arg	gcc Ala	aac Asn	ggt Gly 570	gaa Glu	ttg Leu	gat Asp	gag Glu	cct Pro 575	gag Glu	tac Tyr	ctg Leu	aaa Lys	aag Lys 580	atc Ile	1843
cat His	gcc Ala	aag Lys	aat Asn 585	gcg Ala	gca Ala	gct Ala	Asp	aag Lys 590	gct Ala	tcc Ser	act Thr	gac Asp	aat Asn 595	tct Ser	tcc Ser	1891
act Thr	Asp	aat Asn 600	tct Ser	gaa Glu	gca Ala	Pro.	ggc Gly 605	acc Thr	gat Asp	acg Thr	Asn	caa Gln 610	gag Glu	gag Glu	gag Glu	1939
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Lys

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Arg Ser Ala Thr Pro Lys Leu Gly Ile Asp Leu Gln Gly Gly Thr Arg
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Val Thr Leu Val Pro Gln Gly Gln Asp Pro Thr Gln Asp Gln Leu Asn 35 40 45

Gln Ala Arg Thr Ile Leu Glu Asn Arg Val Asn Gly Met Gly Val Ser 50 60

Gly Ala Ser Val Val Ala Asp Gly Asn Thr Leu Val Ile Thr Val Pro 65 70 75 80

Gly Glu Asn Thr Ala Gln Ala Gln Ser Leu Gly Gln Thr Ser Gln Leu 85 90 95

Leu Phe Arg Pro Val Gly Gln Ala Gly Met Pro Asp Met Thr Thr Leu 100 105 110

Met Pro Glu Leu Glu Glu Met Ala Asn Arg Trp Val Glu Tyr Gly Val 115 120 125

Ile Thr Glu Glu Gln Ala Asn Ala Ser Leu Glu Glu Met Asn Thr Ala 130 135 140

Val Ala Ser Thr Thr Ala Val Glu Glu Glu Glu Ala Thr Glu Pro Glu 145 150 155 160

Pro Val Thr Val Ser Ala Thr Pro Met Asp Glu Pro Ala Asn Ser Ile 165 170 175

Glu Ala Thr Gln Arg Arg Gln Glu Ile Thr Asp Met Leu Arg Thr Asp 180 185 190

Arg Gln Ser Thr Asp Pro Thr Val Gln Ile Ala Ala Ser Ser Leu Met 195 200 205

Gln Cys Thr Thr Asp Glu Met Asp Pro Leu Ala Gly Thr Asp Asp Pro 210 215 220

Arg Leu Pro Leu Val Ala Cys Asp Pro Ala Val Gly Gly Val Tyr Val 225 230 235 240

Leu Asp Pro Ala Pro Leu Leu Asn Gly Glu Thr Asp Glu Glu Asn Gly
245 250 255

Ala Arg Leu Thr Gly Asn Glu Ile Asp Thr Asn Arg Pro Ile Thr Gly 260 265 270

Gly Phe Asn Ala Gln Ser Gly Gln Met Glu Ile Ser Phe Ala Phe Lys 275 280 285

Ser Gly Asp Gly Glu Glu Gly Ser Ala Thr Trp Ser Ser Leu Thr Ser 290 295 300

Gln Tyr Leu Gln Gln Gln Ile Ala Ile Thr Leu Asp Ser Gln Val Ile 305 310 315 320

Ser Ala Pro Val Ile Gln Ser Ala Thr Pro Val Gly Ser Ala Thr Ser 325 330 335 Ile Thr Gly Asp Phe Thr Gin Thr Glu Ala Gln Asp Leu Ala Asn Asn 340 345 350

Leu Arg Tyr Gly Ala Leu Pro Leu Ser Phe Ala Gly Glu Asn Gly Glu 355 360 365

Arg Gly Gly Thr Thr Thr Thr Val Pro Pro Ser Leu Gly Ala Ala Ser 370 375 380

Leu Lys Ala Gly Leu Ile Ala Gly Ile Val Gly Ile Ala Leu Val Ala 385 390 395 400

Ile Phe Val Phe Ala Tyr Tyr Arg Val Phe Gly Phe Val Ser Leu Phe 405 410 415

Thr Leu Phe Ala Ala Gly Val Leu Val Tyr Gly Leu Leu Val Leu Leu 420 425 430

Gly Arg Trp Ile Gly Tyr Ser Leu Asp Leu Ala Gly Ile Ala Gly Leu 435 440 445

Ile Ile Gly Ile Gly Thr Thr Ala Asp Ser Phe Val Val Phe Tyr Glu 450 455 460

Arg Ile Lys Asp Glu Ile Arg Glu Gly Arg Ser Phe Arg Ser Ala Val 465 470 475 480

Pro Arg Ala Trp Glu Ser Ala Lys Arg Thr Ile Val Thr Gly Asn Met
485 490 495

Val Thr Leu Leu Gly Ala Ile Val Ile Tyr Leu Leu Ala Val Gly Glu 500 505 510

Val Lys Gly Phe Ala Phe Thr Leu Gly Leu Thr Thr Val Phe Asp Leu 515 520 525

Val Val Thr Phe Leu Ile Thr Ala Pro Leu Val Ile Leu Ala Ser Arg 530 540

Asn Pro Phe Phe Ala Lys Ser Ser Val Asn Gly Met Gly Arg Val Met 545 550 555 560

Lys Leu Val Glu Glu Arg Arg Ala Asn Gly Glu Leu Asp Glu Pro Glu 565 570 575

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Thr Asp Asn Ser Ser Thr Asp Asn Ser Glu Ala Pro Gly Thr Asp Thr 595 600 605

Asn Gln Glu Glu Glu Lys 610

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Met Asp Leu Asn Thr

1 5

caa cgc tca aag ctc tac gca cag ctt caa ggc cag ctc att gtt tcc 163 Gln Arg Ser Lys Leu Tyr Ala Gln Leu Gln Gly Gln Leu Ile Val Ser 10 15 20

gtg caa gct ccc gac ggc cat gcc atg cga gat acc cat acg ctc acc 211
Val Gln Ala Pro Asp Gly His Ala Met Arg Asp Thr His Thr Leu Thr
25 30 35

cat gtg gcc gca gcc tgt gtc gat ggc ggt gct cct gcc att cgc tgt 259 His Val Ala Ala Ala Cys Val Asp Gly Gly Ala Pro Ala Ile Arg Cys 40 45 50

ggc ggt tac ggc ggt ttg gaa gat atc cgt tca atc tcc aac cgt gtc 307 Gly Gly Tyr Gly Gly Leu Glu Asp Ile Arg Ser Ile Ser Asn Arg Val 55 60 65

gac gtt ccc gtt ttc gga ctc acc aaa gaa ggc tcc gaa gga gtt tac 355
Asp Val Pro Val Phe Gly Leu Thr Lys Glu Gly Ser Glu Gly Val Tyr
70 75 80 85

atc acc cca acc agg gat tcc gtt cga gca gtg gca gaa tcc ggc gcc 403

Ile Thr Pro Thr Arg Asp Ser Val Arg Ala Val Ala Glu Ser Gly Ala
90 95 100

act gta gtc tgc gcg gat gca act ttc cga cct agg cct gac ggc tcc 451 Thr Val Val Cys Ala Asp Ala Thr Phe Arg Pro Arg Pro Asp Gly Ser 105 110 115

acc ttt gca gag ctg gtc act gtt gcc cac gat tcc gga att ctc atc 499
Thr Phe Ala Glu Leu Val Thr Val Ala His Asp Ser Gly Ile Leu Ile
120 125 130

atg gcg gac tgc gca act ccc gaa gaa gtt ctc agt gcg cat aag gct 547 Met Ala Asp Cys Ala Thr Pro Glu Glu Val Leu Ser Ala His Lys Ala 135 140 145

ggc gcg gat ttt gtg tcc acc acg ctt gct gga tac acc gaa cac cgc 595 Gly Ala Asp Phe Val Ser Thr Thr Leu Ala Gly Tyr Thr Glu His Arg 150 165

gag aaa aca gtc ggt cca gat ttc gat tgc ctc cgc gaa gca cgt gag Glu Lys Thr Val Gly Pro Asp Phe Asp Cys Leu Arg Glu Ala Arg Glu

	170	175	16	0
tta gtt ccc gat Leu Val Pro Asp 185	Ala Phe Leu	c att ggc gaa gg 1 Ile Gly Glu Gl 190	yt cgc ttc tcc aa y Arg Phe Ser As 195	c cct 691 n Pro .
gcg gat gtg gcg Ala Asp Val Ala 200	cac ggt cgt His Gly Arg	ctc att ggt go Leu Ile Gly Al 205	c aac gcg atc at a Asn Ala Ile Il 210	c gtg 739 e Val
		Gly Phe Ile Th	t gga cag ttc gc r Gly Gln Phe Al 225	
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Gln Leu Ile Val 20	Ser Val Gln			
Thr His Thr Leu 35	Thr His Val	Ala Ala Ala Cys 40	Val Asp Gly Gly 45	/ Ala
Pro Ala Ile Arg 50	Cys Gly Gly 55	Tyr Gly Gly Leu	Glu Asp Ile Arg	g Ser
Ile Ser Asn Arg	Val Asp Val 70	Pro Val Phe Gly 75		. Gly _80
Ser Glu Gly Val	Tyr Ile Thr 85	Pro Thr Arg Asp 90	Ser Val Arg Ala 95	
Ala Glu Ser Gly A	Ala Thr Val	Val Cys Ala Asp 105	Ala Thr Phe Arg	Pro
Arg Pro Asp Gly S		Ala Glu Leu Val 120	Thr Val Ala His 125	Asp
Ser Gly Ile Leu I 130	le Met Ala A 135	Asp Cys Ala Thr	Pro Glu Glu Val 140	Leu
Ser Ala His Lys A	Ala Gly Ala <i>F</i> 150	Asp Phe Val Ser 155	Thr Thr Leu Ala	Gly 160

Tyr Thr Glu His Arg Glu Lys Thr Val Gly Pro Asp Phe Asp Cys Leu 165 170 175

185 Arg Phe Ser Asn Pro Ala Asp Val Ala His Gly Arg Leu Ile Gly Ala 200 Asn Ala Ile Ile Val Gly Thr Ala Ile Thr Asp Pro Gly Phe Ile Thr 215 Gly Gln Phe Ala Ser Leu Leu His <210> 61 <211> 1219 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (48)..(1196) <223> RXN01863 <400> 61 ggtatcatac cgatatgaac caaatagaaa gaaggaagtt taagacgatg aat agc 56 Met Asn Ser gtc aaa ttg aag caa cct gtt agc att tac aat gat cca tgg gaa tca Val Lys Leu Lys Gln Pro Val Ser Ile Tyr Asn Asp Pro Trp Glu Ser tat aac gat gtt aaa gaa cat ggc caa tta act tta agt aac atc gaa Tyr Asn Asp Val Lys Glu His Gly Gln Leu Thr Leu Ser Asn Ile Glu ttt aca act aca aat ctt tgt aat atg cgt tgt agc cac tgt gca gtt 200 Phe Thr Thr Asn Leu Cys Asn Met Arg Cys Ser His Cys Ala Val ggt tat act tta caa act gtc gac ccc gag cct tta gat atg gac tta 248 Gly Tyr Thr Leu Gln Thr Val Asp Pro Glu Pro Leu Asp Met Asp Leu att tat cgt aga ctt gat gaa att cca aat ctg cga acg atg tca att 296 Ile Tyr Arg Arg Leu Asp Glu Ile Pro Asn Leu Arg Thr Met Ser Ile aca ggt ggc gaa cca atg ttt tct aaa aag tct att aga aat gtt gtt Thr Gly Gly Glu Pro Met Phe Ser Lys Lys Ser Ile Arg Asn Val Val aaa cct cta tta aag tat gca cat cat cga ggt ata tat aca caa atg 392 Lys Pro Leu Lys Tyr Ala His His Arg Gly Ile Tyr Thr Gln Met 105

Arg Glu Ala Arg Glu Leu Val Pro Asp Ala Phe Leu Ile Gly Glu Gly

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aa As:	t tc n Se	a aa r As	c ct n Le	a ac u Th 12	r Le	g cci u Pro	caa Glr	a gat n Asp	cgt Arg 125	Ty	t tta r Le	a gat u Asj	t at	t gc e Ala 13	gaa a Glu	440	
ta: Ty:	t ate	c ga e As	t gt p Va. 13	1 Me	g ca t Hi	t ato s Ile	tca Ser	cat His	s Asr	tge Tr	g gga p Gly	a aca y Thi	a act	r As	t gaa p Glu	488	
			n Val					Met					Pro		a aaa 1 Lys	536	
		Le					Gln					Ala			tta Leu	584 .	
	Glu					e Val					Met				agt Ser 195	632	
					Arg										atg Met	680	
				His										Phe	gca Ala	728	
agt Ser	caa Gln	tta Leu 230	Asn	gtg Val	tta Leu	act Thr	cta Leu 235	gcg Ala	gaa Glu	atg Met	aaa Lys	aag Lys 240	aca Thr	att	cat His	776	
						gat Asp 250										824	
Leu 260	Pro	Val	Phe	Pro	Cys 265	tta Leu	Lys	Asp	Asp	Glu 270	Asp	Gln	Lys	Leu	Leu 275	872	
Ser	Arg	Leu	Arg	Asn 280	Ala	aac Asn	Asn	Val	Thr 285	Thr	Arg	Asn	Asp	Pro 290	Asp	920	
						gtc Val	Asn									968	
Thr	Asp	Phe 310	Gly	Asp	Glu		Gly ' 315	Thr	Ile	Ser	Asn	11e 320	Gln	Lys	Asp	1016	
					Phe	gat Asp : 330				Ser						1064	

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WO 01/00804 PCT/IB00/00922

Ser Leu Asn Cys His Cys Ser Glu Phe Ser Cys Leu Gly Pro Asn Val 340 345 350 355

ctt gtt aaa aat atg tac tat ccg aat atg gat ttt aaa gat aat gag 1160 Leu Val Lys Asn Met Tyr Tyr Pro Asn Met Asp Phe Lys Asp Asn Glu 360 365 370

cgt cat atg cac aaa caa cca caa att ata caa ttt taaaaactct 1206 Arg His Met His Lys Gln Pro Gln Ile Ile Gln Phe

taattatgcg gag 1219

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Trp Glu Ser Tyr Asn Asp Val Lys Glu His Gly Gln Leu Thr Leu Ser 20 25 30

Asn Ile Glu Phe Thr Thr Asn Leu Cys Asn Met Arg Cys Ser His
35 40 45

Cys Ala Val Gly Tyr Thr Leu Gln Thr Val Asp Pro Glu Pro Leu Asp 50 55 60

Met Asp Leu Ile Tyr Arg Arg Leu Asp Glu Ile Pro Asn Leu Arg Thr 65 70 75 80

Met Ser Ile Thr Gly Gly Glu Pro Met Phe Ser Lys Lys Ser Ile Arg 85 90 95

Asn Val Val Lys Pro Leu Leu Lys Tyr Ala His His Arg Gly Ile Tyr 100 105 110

Thr Gln Met Asn Ser Asn Leu Thr Leu Pro Gln Asp Arg Tyr Leu Asp 115 120 125

Ile Ala Glu Tyr Ile Asp Val Met His Ile Ser His Asn Trp Gly Thr 130 135 140

Thr Asp Glu Phe Ala Asn Val Gly Phe Gly Ala Met Lys Lys Gln Pro 145 150 155 160

Pro Leu Lys Ala Lys Leu Lys Leu Tyr Glu Gln Met Ile Ser Asn Ala 165 170 175

Arg Thr Leu Ser Glu Gln Gly Met Phe Val Ser Ala Glu Thr Met Leu 180 185 190

Asn Gln Ser Thr Leu Pro His Leu Arg Lys Ile His Gln Glu Val Val

195 200 205

His Asp Met Lys Cys Ser Arg His Glu Ile His Pro Met Tyr Pro Ala 210 - 215 220

Asp Phe Ala Ser Gln Leu Asn Val Leu Thr Leu Ala Glu Met Lys Lys 225 230 235 240

Thr Ile His Asp Ile Leu Asp Phe Arg Asp Glu Asp Ile Trp Met Leu 245 250 255

Phe Gly Thr Leu Pro Val Phe Pro Cys Leu Lys Asp Asp Glu Asp Gln 260 265 270

Lys Leu Leu Ser Arg Leu Arg Asn Ala Asn Asn Val Thr Thr Arg Asn 275 280 285

Asp Pro Asp Gly Arg Ser Arg Leu Asn Val Asn Val Phe Thr Gly Asn 290 295 300

Val Ile Val Thr Asp Phe Gly Asp Glu Thr Gly Thr Ile Ser Asn Ile 305 310 315 320

Gln Lys Asp Lys Leu Thr Asp Val Phe Asp Lys Trp Leu Ser Ser Asp 325 330 335

Leu Ala Lys Ser Leu Asn Cys His Cys Ser Glu Phe Ser Cys Leu Gly 340 345 350

Pro Asn Val Leu Val Lys Asn Met Tyr Tyr Pro Asn Met Asp Phe Lys 355 360 365

Asp Asn Glu Arg His Met His Lys Gln Pro Gln Ile Ile Gln Phe 370 375 380

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Met Ala Lys Thr His
1 5

ttt caa ggc aac gaa act gct acc tcc ggc gaa ctg cca cag gtc ggc 163 Phe Gln Gly Asn Glu Thr Ala Thr Ser Gly Glu Leu Pro Gln Val Gly 10 15 20

	W	O 01/	/00 8 04	ı	•											PCT/IB00/00922
gac Asp	aac Asn	ctc Leu	gca Ala 25	Glu	tto Phe	aac Asn	ctc Leu	gtc Val 30	Asn	acc Thr	gaa Glu	ctg Leu	ggc Gly 35	Glu	gtc Val	211
			Asp			ggc							Ile			
		Asp				tgt Cys 60						Lys				
gca Ala 70	gca Ala	gca Ala	agc Ser	ctg Leu	gaa Glu 75	aac Asn	acc Thr	acc Thr	gtg Val	ctg Leu 80	tgc Cys	atc Ile	tcc Ser	aag Lys	gat Asp 85	355
ctt Leu	cca Pro	ttc Phe	gca Ala	ctg Leu 90	ggc	cgt Arg	ttc Phe	tgc Cys	tcc Ser 95	gca Ala	gaa Glu	ggc Gly	atc Ile	gag Glu 100	aac Asn	403
gtc Val	acc Thr	cca Pro	gta Val 105	tcc Ser	gca Ala	ttc Phe	cgt Arg	tcc Ser 110	acc Thr	ttc Phe	ggt Gly	gaa Glu	gac Asp 115	aac Asn	ggc Gly	451
atc Ile	gtg Val	ctc Leu 120	gaa Glu	ggc Gly	tca Ser	cca Pro	ctt Leu 125	aag Lys	ggt Gly	ctt Leu	ctt Leu	gca Ala 130	cgc Arg	agc Ser	gtc Val	499
atc Ile	gtc Val 135	gtc Val	gat Asp	gaa Glu	aac Asn	ggc Gly 140	aag Lys	gtt Val	gct Ala	tac Tyr	acc Thr 145	cag Gln	ttg Leu	gtt Val	gat Asp	547
gag Glu 150	atc Ile	ttc Phe	act Thr	Glu	cct Pro 155	gat Asp	tac Tyr	gac Asp	gct Ala	gca Ala 160	ctt Leu	gct Ala	ggg Gly	ctg Leu	aac Asn 165	595
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Glu Leu Gly Glu Val Ser Ser Lys Asp Phe Gln Gly Arg Lys Leu Val 35

Leu Asn Ile Phe Pro Ser Val Asp Thr Gly Val Cys Ala Thr Ser Val 50 55

Arg Lys Phe Asn Glu Ala Ala Ser Leu Glu Asn Thr Thr Val Leu 70 Cys Ile Ser Lys Asp Leu Pro Phe Ala Leu Gly Arg Phe Cys Ser Ala Glu Gly Ile Glu Asn Val Thr Pro Val Ser Ala Phe Arg Ser Thr Phe Gly Glu Asp Asn Gly Ile Val Leu Glu Gly Ser Pro Leu Lys Gly Leu Leu Ala Arg Ser Val Ile Val Val Asp Glu Asn Gly Lys Val Ala Tyr Thr Gln Leu Val Asp Glu Ile Phe Thr Glu Pro Asp Tyr Asp Ala Ala 155 Leu Ala Gly Leu Asn <210> 65 <211> 879 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (101)..(856) <223> RXN01676 <400> 65 agttacaget ttteteggtg geacactege getaettage cettgtgeeg cacteettt 60 accagcattt tttgcatcct cagtgggtgc tggcccgcgc atg atc ctt cac ggt Met Ile Leu His Gly gtt gtg ttc tac gca gga ctt cta gta ctt ctc gtg cca ctt ggc ctt 163 Val Val Phe Tyr Ala Gly Leu Leu Val Leu Leu Val Pro Leu Gly Leu ggt gcg gga atc ctc ggc gag ctg ttt atc acc caa cgc cag acc atc Gly Ala Gly Ile Leu Gly Glu Leu Phe Ile Thr Gln Arg Gln Thr Ile atc gtg gtt tca tcg atc gtg ctg att atc cta ggt ttt gtc cag atc 259 Ile Val Val Ser Ser Ile Val Leu Ile Ile Leu Gly Phe Val Gln Ile ttc ggc ggc gga ttc gac ttc gga aaa gca ctc cca gga tta gat cgt 307 Phe Gly Gly Gly Phe Asp Phe Gly Lys Ala Leu Pro Gly Leu Asp Arg ctg caa tot aag goo act gtg acc toa ggt ota gga aag ago ttt tta 355 Leu Gln Ser Lys Ala Thr Val Thr Ser Gly Leu Gly Lys Ser Phe Leu

80

85

										-					•	
ct. Le	a gg u Gl	a at	g ac t Th	c agt r Sei 90	r Sez	att Ile	gcc Ala	ggt Gly	tti Phe	e Cys	t tco s Ser	gga Gly	cca Pro	ato Ile 100	ctc Leu	403
gg:	c gco y Ala	c gti a Vai	t ct: l Le: 10:	u Thi	ttg Leu	gct Ala	gcc Ala	Thr	Se	gga Gly	a aac / Asn	tcc Ser	ato Ile 115	Thr	tca Ser	451
gca Ala	a cto a Leu	2 att 1 Ile 120	e Let	g agt 1 Ser	gct Ala	tat Tyr	ggt Gly 125	Ala	gga	atg Met	g gtg : Val	ctg Leu 130	Pro	ctg Leu	atg Met	499
gct Ala	: att	e Ala	a gcg a Ala	g ctc Leu	tgg Trp	gcc Ala 140	aaa Lys	ctc Leu	gga Gly	cag Gln	cgt Arg 145	gga Gly	cag Gln	cag Gln	atg Met	547
Leu 150	Arg	Gly	' Arg	gaa Glu	Phe 155	Thr	Phe	Leu	Gly	Arg 160	Gln	Trp	His	Ile	Val 165	595
tct Ser	gtc Val	att Ile	agc Ser	ggt Gly 170	gcc Ala	ctg Leu	atc Ile	atc Ile	gct Ala 175	gtc Val	gga Gly	atc Ile	ctc Leu	ttt Phe 180	tgg Trp	643
Ser	Thr	Asn	Gly 185	ctt Leu	Val	Ser	Met	Pro 190	Glu	Leu	Val	Pro	Met 195	Asp	Thr	691
Gln	Ile	Trp 200	Leu	cag Gln	Glu	Ala	Thr 205	Phe	Ser	Leu	Gly	Ser 210	Pro	Leu	Phe	739
Asp	Ile 215	Ala	Leu	atc Ile	Ile	Val 220	Ala	Ala	Gly	Leu	Phe 225	Leu	Tyr	Phe	Trp	7 87
Asn 230	Lys	Arg	Gln		Arg 235	Lys (Glu (Glu .	Ala	Gln 240	Arg	Pro	Lys	gaa Glu	agt Ser 245	835
gga Gly	tgg Trp	gtt Val	Ile	aac Asn 250	ect (Pro /	cgc (Arg	taat	tatt	ag t	tttg	gagc	g ag	g			879

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<211> 252

<212> PRT

<213> Corynebacterium glutamicum

<400> 66

Met Ile Leu His Gly Val Val Phe Tyr Ala Gly Leu Leu Val Leu Leu 1 5 10 15

Val Pro Leu Gly Leu Gly Ala Gly Ile Leu Gly Glu Leu Phe Ile Thr

Gln Arg Gln Thr Ile Ile Val Val Ser Ser Ile Val Leu Ile Ile Leu 35 40 45

Gly Phe Val Gln Ile Phe Gly Gly Gly Phe Asp Phe Gly Lys Ala Leu 50 55 60

Pro Gly Leu Asp Arg Leu Gln Ser Lys Ala Thr Val Thr Ser Gly Leu 65 70 75 80

Gly Lys Ser Phe Leu Leu Gly Met Thr Ser Ser Ile Ala Gly Phe Cys 85 90 95

Ser Gly Pro Ile Leu Gly Ala Val Leu Thr Leu Ala Ala Thr Ser Gly 100 105 110

Asn Ser Ile Thr Ser Ala Leu Ile Leu Ser Ala Tyr Gly Ala Gly Met 115 120 125

Val Leu Pro Leu Met Ala Ile Ala Ala Leu Trp Ala Lys Leu Gly Gln 130 135 140

Arg Gly Gln Gln Met Leu Arg Gly Arg Glu Phe Thr Phe Leu Gly Arg 145 150 155 160

Gln Trp His Ile Val Ser Val Ile Ser Gly Ala Leu Ile Ile Ala Val 165 170 175

Gly Ile Leu Phe Trp Ser Thr Asn Gly Leu Val Ser Met Pro Glu Leu 180 185 190

Val Pro Met Asp Thr Gln Ile Trp Leu Gln Glu Ala Thr Phe Ser Leu 195 200 205

Gly Ser Pro Leu Phe Asp Ile Ala Leu Ile Ile Val Ala Ala Gly Leu 210 220

Phe Leu Tyr Phe Trp Asn Lys Arg Gln Lys Arg Lys Glu Glu Ala Gln 225 230 235 240

Arg Pro Lys Glu Ser Gly Trp Val Ile Asn Pro Arg 245 250

<210> 67

<211> 744

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<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (101)..(721)

<223> RXN00380

<400> 67

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cg	tgca	ttac	aac	gaac	cag (ctca	ggag	at t	tgat	cacto		Arg			aaa Lys 5	115
					e Gl					u Sei					gta Val	163
				r Ası					y Thi					Val	ggc Gly	211
			e Glı					Asp					Ile		tac Tyr	259
		ı Ala					Leu					Gly			ctc Leu	307
	Glu					Ile				gat Asp 80						355
					Trp					gca Ala						403
				Gln						ctc Leu						451
			Pro							atc Ile						499
										gac Asp						547
										gca Ala 160						595
										gtg Val						643
							Arg.			acc Thr		Lys				691
	Val			cca Pro		Val .				taaa	tgtc	tg a	gatt	gtgg	rt	741

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<210> 68

<211> 207

<212> PRT

<213> Corynebacterium glutamicum

<400> 68

Val Arg Leu Thr Lys Leu Ala Ala Thr Ile Gly Cys Val Thr Leu Ser

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Gly Leu Ala Leu Val Ala Cys Ser Ser Asp Ser Thr Ala Gly Thr Asp 20 25 30

Ala Val Ala Val Gly Gly Thr Phe Gln Phe His Ser Pro Asp Gly Lys 35 40 45

Met Glu Ile Phe Tyr Asp Glu Ala Asp Arg Gln Gln Leu Pro Asp Ile 50 55 60

Gly Gly Asp Ser Leu Met Glu Glu Gly Thr Gln Ile Asn Leu Ser Asp 65 70 75 80

Phe Glu Asn Gln Val Val Ile Leu Asn Ala Trp Gly Gln Trp Cys Ala 85 90 95

Pro Cys Arg Ser Glu Ser Asp Asp Leu Gln Ile Ile His Glu Glu Leu 100 105 110

Gln Ala Ala Gly Asn Gly Asp Thr Pro Gly Gly Thr Val Leu Gly Ile 115 120 125

Asn Val Arg Asp Tyr Ser Arg Asp Ile Ala Gln Asp Phe Val Thr Asp 130 135 140

Asn Gly Leu Asp Tyr Pro Ser Ile Tyr Asp Pro Pro Phe Met Thr Ala 145 150 155 160

Ala Ser Leu Gly Gly Val Pro Ala Ser Val Ile Pro Thr Thr Ile Val 165 170 175

Leu Asp Lys Gln His Arg Pro Ala Ala Val Phe Leu Arg Glu Val Thr 180 185 190

Ser Lys Asp Val Leu Asp Val Ala Leu Pro Leu Val Asp Glu Ala 195 200 205

<210> 69

<211> 495

<212> DNA

<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (101)..(472)

<223> RXN00937

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- tctatatata gaccttacaa atcttgaacg gagattctta atg gca acc atc gat 119
 Met Ala Thr Ile Asp
 1 5
- gta acc gaa gaa aca ttt gag agc aca gtt acc ggc gac gga att gtc 163 Val Thr Glu Glu Thr Phe Glu Ser Thr Val Thr Gly Asp Gly Ile Val 10 15 20
- ctc gta gac gca tgg gca tcc tgg tgc gga cct tgc cgc cag ttc gcc 211 Leu Val Asp Ala Trp Ala Ser Trp Cys Gly Pro Cys Arg Gln Phe Ala 25 30 35
- cca acc tac gag aag gtt tcc gaa acc cac acc gac gca acc ttc gcc 259
 Pro Thr Tyr Glu Lys Val Ser Glu Thr His Thr Asp Ala Thr Phe Ala
 40 45 50
- aag ctt gat acc gaa gca aac cag ggc ctg gct gca gca ctg cag atc 307 Lys Leu Asp Thr Glu Ala Asn Gln Gly Leu Ala Ala Leu Gln Ile 55 60 65
- cag tcc atc cca act ctg atg gtt ttc cgc gac ggc atc atg gtc tac 355 Gln Ser Ile Pro Thr Leu Met Val Phe Arg Asp Gly Ile Met Val Tyr 70 75 80 85
- cgc gaa gcc ggc acc atg cca gct cct gca ctg gat gat ctg gtc aac 403 Arg Glu Ala Gly Thr Met Pro Ala Pro Ala Leu Asp Asp Leu Val Asn 90 95 100
- cag gtt aag gca ctc gac atg gat gac gtt cgt cgc cag gtc gca gag 451 Gln Val Lys Ala Leu Asp Met Asp Asp Val Arg Arg Gln Val Ala Glu 105
- cag cag ggt tct gca gag gca taagcttcca attgtgtttt ggt
 Gln Gln Gly Ser Ala Glu Ala
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<210> 70

<211> 124

<212> PRT

<213> Corynebacterium glutamicum

<400> 70

Met Ala Thr Ile Asp Val Thr Glu Glu Thr Phe Glu Ser Thr Val Thr

Gly Asp Gly Ile Val Leu Val Asp Ala Trp Ala Ser Trp Cys Gly Pro 20 25 30

Cys Arg Gln Phe Ala Pro Thr Tyr Glu Lys Val Ser Glu Thr His Thr 35 40 45

		w	O 01/	00804								-					PCT/IB00/00922
	Asp	Ala 50	Thr	Phe	Ala	Lys	Leu 55	Asp	Thr	Glu	Ala	Asn 60	Gln	Gly	Leu	Ala	
į	Ala 65	Ala	Leu	Gln	Ile	Gln 70	Ser	Ile	Pro	Thr	Leu 75	Met	Val	Phe	Arg	Asp 80	
(Gly	Ile	Met	Val	Tyr	Arg	Glu	Ala	Gly	Thr	Met	Pro	Ala	Pro	Ala	Leu	•

90

Asp Asp Leu Val Asn Gln Val Lys Ala Leu Asp Met Asp Asp Val Arg 100 105 110

95

Arg Gln Val Ala Glu Gln Gln Gly Ser Ala Glu Ala 115 120

85

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tgcacccgtc taatgaaaat cattactatt aggtgtcatg atg gac cat gca cac 115

Met Asp His Ala His

1 5

gat tcc tgc tca cca act ctg cgc cgt gat ttg gag gtc act ggc cag 163
Asp Ser Cys Ser Pro Thr Leu Arg Arg Asp Leu Glu Val Thr Gly Gln
10 15 20

ctc caa cct gag aaa gct gtc gat tta gca gcg ccg cac gaa ggg aag 211 Leu Gln Pro Glu Lys Ala Val Asp Leu Ala Ala Pro His Glu Gly Lys 25 30 35

gtt gcc aat ata acg aag gtg acc tcc tca aat atg gag cac acc atc 259
Val Ala Asn Ile Thr Lys Val Thr Ser Ser Asn Met Glu His Thr Ile
40 45 50

acg cag gcc tca aaa gct aag gag gtg gtg gtg ctc att ggt cac tcc 307 Thr Gln Ala Ser Lys Ala Lys Glu Val Val Val Leu Ile Gly His Ser 55 60 65

ctg ctg ccc aca ttt cag gat ttg gaa aaa gac att ctg cac ttt cag 355 Leu Leu Pro Thr Phe Gln Asp Leu Glu Lys Asp Ile Leu His Phe Gln 70 75 80 85

gca ggt aat aaa ggg cga ttt tct gta gcg att gtt gat cct gat cgc 403 Ala Gly Asn Lys Gly Arg Phe Ser Val Ala Ile Val Asp Pro Asp Arg 90 95 100

	1	VO 01	1/0080	4)						4	PCT/IB00/00922
			gtg Val 105	. Val				Pro				Val	451
			aaa Lys				Ile				Ser		499
		Pro	gtt Val							Ser			547
			gaa Glu		Gly								595
			gca Ala										643
			tat Tyr 185										691
			gtg Val										739
			atc Ile										787
			gcg Ala										835
			cac His										883
			gag Glu 265			Leu							931
ttg Leu	Glu				Val (taag	aaaa	ca	977
cttt	aaat	at t	ct										990

<210> 72 <211> 289 <212> PRT <213> Corynebacterium glutamicum

<400> 72

Met Asp His Ala His Asp Ser Cys Ser Pro Thr Leu Arg Arg Asp Leu
1 5 10 15

Glu Val Thr Gly Gln Leu Gln Pro Glu Lys Ala Val Asp Leu Ala Ala 20 25 30

Pro His Glu Gly Lys Val Ala Asn Ile Thr Lys Val Thr Ser Ser Asn 35 40 45

Met Glu His Thr Ile Thr Gln Ala Ser Lys Ala Lys Glu Val Val Val 50 55 60

Leu Ile Gly His Ser Leu Leu Pro Thr Phe Gln Asp Leu Glu Lys Asp 65 70 75 80

Ile Leu His Phe Gln Ala Gly Asn Lys Gly Arg Phe Ser Val Ala Ile 85 90 95

Val Asp Pro Asp Arg Ser Ala Asp Val Val Ala Arg Phe Arg Pro Lys 100 105 110

Gln Ile Pro Val Ala Tyr Val Val Lys Asp Gly Ala Ser Ile Ala Glu 115 120 125

Phe Asn Ser Leu Asn Lys Glu Pro Val Ala Gln Trp Leu Asp His Phe 130 135 140

Val Ser Arg Glu Thr Ile Pro Asn Glu Lys Glu Gly Asp Val Asp Lys 145 150 155 160

Gln Ile Asp Pro Arg Leu Trp Arg Ala Ala Glu Leu Val Asn Ala Gly 165 170 175

Asp Phe Arg Ala Ala Leu Ala Leu Tyr Glu Gln Leu Pro Gln Asp Ala 180 185 190

Thr Val Lys Arg Ala His Ala Ala Val Ser Val Leu Ala Arg Met Ser 195 200 205

Val Ala Asp Arg Gly Glu Asp Pro Ile Glu Lys Ser Arg Arg Asp Pro 210 215 220

Asp Asp Val Asn Lys Ala Leu Ala Ala Ala Asp Met Tyr Val Leu Met 225 230 235 240

Asn Gln Pro Asp Thr Ala Leu Ala His Leu Ala Ala Leu Leu Pro Lys 245 250 255

Pro Glu Ala Ala Arg Arg Ile Val Glu Leu Leu Asn Leu Phe Asp Pro 260 265 270

Leu Asp Leu Val Ala Leu Glu Ile Arg Ala Gln Val Gly Asn Ala Met 275 280 285

Ser

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	00> cca		tcc	ctca	agg ·	tgtg	aagat	ta c	ggtt	aggat	t aga	aaaa	gaat	tttt	ttgad	g 60
tt	ggaca	attc	tcaa	aaato	caa (gtag	caago	gg at	caa	actct		Ser			aag Lys 5	115
					n Ala					ı Glü					agc Ser	163
				Glu					Leu					Ala	tcc Ser	211
ctg Leu	gct Ala	gto Val 40	. Ile	ctg Leu	gtt Val	gtc Val	gtt Val 45	Gly	ggt Gly	ato Ile	tgg Trp	tac Tyr 50	Ala	gct Ala	acc Thr	259
cgc Arg	agc Ser 55	Thr	gaa Glu	gac Asp	gaa Glu	gtc Val 60	Ile	acc	gct Ala	gat Asp	gaa Glu 65	Thr	tcc Ser	acc Thr	acc	307
															gcg Ala 85	355
ctc Leu	ggc Gly	gac Asp	tcc Ser	gtg Val 90	acc Thr	tgt Cys	gag Glu	tac Tyr	cca Pro 95	gat Asp	gct Ala	ggc Gly	gag Glu	gct Ala 100	tcc Ser	403
							act Thr									451
							gcc Ala 125									499
							acc Thr									547
tcc Ser 150	gag Glu	ggc Gly	tac Tyr	Tyr	aac Asn 155	gat Asp	act Thr	gtc Val	tgc Cys	cac His 160	cgc Arg	atc Ile	acc Thr	acc Thr	tct Ser 165	595

<210> 74

<212> PRT

<213> Corynebacterium glutamicum

<400> 74

Val Ser Thr Asn Lys Glu Arg Arg Gln Gln Ala Leu Ser Gln Leu Glu

Lys Glu Ile Lys Ser Arg Asp Arg Lys Glu Lys Thr Lys Pro Leu Thr

Val Val Phe Ala Ser Leu Ala Val Ile Leu Val Val Val Gly Gly Ile

Trp Tyr Ala Ala Thr Arg Ser Thr Glu Asp Glu Val Ile Thr Ala Asp

Glu Thr Ser Thr Thr Ala Glu Thr Pro Asp Tyr Gln Pro Leu Ala Leu

Thr Arg Thr Thr Ala Leu Gly Asp Ser Val Thr Cys Glu Tyr Pro Asp

Ala Gly Glu Ala Ser Lys Asp Val Ser Lys Pro Ala Thr Glu Asn Val

Pro Ala Thr Gly Thr Val Thr Val Asn Leu Thr Thr Ala Gln Gly Asn 120

192

240

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Ile	Gly 130		Glu	Let	Asp	Arg 135		Va.	l Se	r Pro	o Cy:		· Val	l Asr	Ala	
Val 145	Glu	His	Met	Ala	Ser 150		Gly	ту	г Ту	r Ası 15		o Thr	Va]	l Cys	His 160	
Arg	Ile	Thr	Thr	Ser 165		Ile	Tyr	Va]	l Le		n Cys	s Gly	/ Asp	Pro 175	Ser	
Ser	Thr	Gly	Ala 180	Gly	Gly	Pro	Gly	Phe 185		r Phe	≥ Ala	a Asn	Glu 190		Pro	
Thr	Asp	Glu 195	Ala	Thr	Asp	Leu	Thr 200	Thr	Pro	o Val	Ile	Tyr 205		Arg	Gly	
Thr	Ile 210	Ala	Met	Ala	Asn	Ala 215	Gly	Ala	Asp	Thr	220	_	Leu	Pro	Val	
Leu 225	Pro	Gln	Leu	Arg	Gly 230	Phe	Pro	Thr	G13	/ Thr 235		Leu	His	Leu	Leu 240	
Arg	Pro	Asp	His	Arg 245	Arg	Arg	Pro	Cys	Asn 250		Arg	Arg	His	Arg 255	_	
Ser	Trp	His														
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<220: <221: <222: <223:	> CD: > (1) (-													
<400>															•	
ctg c Leu A 1																4 8
gtc t /al T	gg a	aaa (Lys <i>l</i>	gcc (Ala / 20	gcc a	acc (Thr (gaa g Glu G	gaa o Slu <i>l</i>	gca Ala 25	gaa Glu	ctc Leu	ctc Leu	gca Ala	gct Ala 30	gac Asp	ggc Gly	96
gcc g Ala V	tc c	ac q lis A 35	sp (ag g Sln (gaa o Slu I	tc t Leu P	tc o he I 40	ctc Leu	aac Asn	tgc Cys	acc Thr	acc Thr 45	tcc Ser	cca Pro	ctg Leu	. 14

atc ttc gcc tcc gcg atg ctc aac ttc ggc gtc cac caa atc ctg gac Ile Phe Ala Ser Ala Met Leu Asn Phe Gly Val His Gln Ile Leu Asp

acc etc tge caa etc gea eea tee eec gee gge ege gae gea gae eec

55

	1	VO 01	1/0080	14												PCT/IB00/00922
Thr 65		ı Cys	Glr	Leu	Ala 70		Ser	Pro	Ala	Gly 75		Asp	Ala	Asp	Pro 80	
	_		_	-	Ala			•	_	Asp	-		-	_	acc	288
				Ser					Lys						gac Asp	336
			Arg												gaa Glu	384
	-	_		-		_							cgc Arg	_	ttc Phe	432
				_			-			_		-	tct Ser		_	480
													gcc Ala			528
										_			caa Gln 190		cca Pro	576
	-						_			-		_	cgc Arg	_		624
Ser	ctc Leu 210	ggc Gly	aaa Lys	tac Tyr	aaa Lys	cag Gln 215	ttc Phe	cgc Arg	aaa Lys	gcc Ala	ctc Leu 220	gag Glu	cag Gln	ctg Leu	gac Asp	672
				Val					Asn				ggc Gly			720
aac Asn			His	,		_										741

<210> 76 <211> 247 <212> PRT <213> Corynebacterium glutamicum

Val Trp Lys Ala Ala Thr Glu Glu Ala Glu Leu Leu Ala Ala Asp Gly
20 25 30

Ala Val His Asp Gln Glu Leu Phe Leu Asn Cys Thr Thr Ser Pro Leu 35 40 45

Ile Phe Ala Ser Ala Met Leu Asn Phe Gly Val His Gln Ile Leu Asp 50 55 60

Thr Leu Cys Gln Leu Ala Pro Ser Pro Ala Gly Arg Asp Ala Asp Pro 65 70 75 80

Lys-Ala Leu Glu Ala Ala Thr Ser Ala Met Asp Asp His Arg Asp Thr 85 90 95

Thr Asp Asp Phe Ser Gly Val Val Phe Lys Val Gln Ala Gly Met Asp 100 105 110

Lys Asn His Arg Asp Thr Leu Ala Phe Met Arg Val Val Ser Gly Glu 115 120 125

Phe Asp Arg Gly Met Gln Val Thr His Ser Gln Ser Gly Arg Ser Phe 130 135 140

Ser Thr Lys Tyr Ala Leu Thr Val Phe Gly Arg Thr Arg Ser Thr Val 145 150 155 160

Glu Thr Ala Phe Pro Gly Asp Ile Val Gly Leu Val Asn Ala Gly Ala 165 170 175

Leu Ala Pro Gly Asp Thr Ile Phe Glu Gly Arg Lys Ile Gln Tyr Pro 180 . 185 190

Pro Met Pro Lys Phe Ala Pro Glu His Phe Arg Ile Leu Arg Ala Lys 195 200 205

Ser Leu Gly Lys Tyr Lys Gln Phe Arg Lys Ala Leu Glu Gln Leu Asp 210 215 220

Ser Glu Gly Val Val Gln Ile Leu Lys Asn Asp Leu Arg Gly Asp Ala 225 230 235 240

Asn Pro Gly His Gly Arg Cys 245

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<222> (101)..(478)

<223> RXN02002

<400> 77

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					Ala					cgc Arg						163
				Asp						ctc Leu						211
ctg Leu	cat His	gca Ala 40	His	atc Ile	atc Ile	tcc Ser	gaa Glu 45	gcc Ala	ggc Gly	gcc Ala	acc Thr	cac His 50	ggc Gly	aaa Lys	gca Ala	259
ggc Gly	cgc Arg 55	aaa Lys	gcc Ala	acc Thr	gtt Val	tcc Ser 60	gac Asp	tgg Trp	atg Met	gaa Glu	atg Met 65	gaa Glu	aaa Lys	gac Asp	cgc Arg	307
										ttc Phe 80						355
										ctc Leu						403
										gtc Val						451
					atg Met											478

<210> 78

<211> 126

<212> PRT

<213> Corynebacterium glutamicum

<400> 78

Met Ser Asn Ala Asn Ser Asp Thr Thr Ala Ala Glu Ala His Arg Arg
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Arg Thr Phe Ala Val Ile Ala His Pro Asp Ala Gly Lys Ser Thr Leu 20 25 30

Thr Glu Ala Leu Ala Leu His Ala His Ile Ile Ser Glu Ala Gly Ala
35 40 45

Thr His Gly Lys Ala Gly Arg Lys Ala Thr Val Ser Asp Trp Met Glu 50 55 60

Met Glu Lys Asp Arg Gly Ile Ser Ile Ala Ser Ser Ala Leu Gln Phe 70 Glu Tyr Ala Pro Glu Gly His Ala Gly Glu Pro Phe Met Ile Asn Leu 90 Val Asp Thr Pro Gly His Ala Asp Phe Ser Glu Asp Thr Tyr Arg Val Leu Met Ala Val Asp Ala Ala Val Met Leu Met His Ser Val <210> 79 <211> 1080 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (101)..(1057) <223> RXN02736 <400> 79 cagaggatta cccagcgggt acgtggggtc caaagagcgc tgatgaaatg ctttcccqca 60 acggtcacac ctggcgcagg ccataattta ggggcaaaaa atg atc ttt qaa ctt Met Ile Phe Glu Leu 1 ccg gat acc acc cag caa att tcc aag acc cta act cga ctg cgt 163 Pro Asp Thr Thr Gln Gln Ile Ser Lys Thr Leu Thr Arg Leu Arg 15 gaa tog ggc acc cag gtc acc acc ggc cga gtg ctc acc ctc atc gtg 211 Glu Ser Gly Thr Gln Val Thr Thr Gly Arg Val Leu Thr Leu Ile Val 30 gtc act gac tcc gaa agc gat gtc gct gca gtt acc gag tcc acc aat 259 Val Thr Asp Ser Glu Ser Asp Val Ala Ala Val Thr Glu Ser Thr Asn 40 gaa goo tog oge gag cac coa tot oge gtg ato att ttg gtg gtt gge 307 Glu Ala Ser Arg Glu His Pro Ser Arg Val Ile Ile Leu Val Val Gly 55 gat aaa act gca gaa aac aaa gtt gac gca gaa gtc cgt atc ggt ggc Asp Lys Thr Ala Glu Asn Lys Val Asp Ala Glu Val Arg Ile Gly Gly 70 gac get ggt get tee gag atg ate ate atg cat etc aac gga eet gte 403

Asp Ala Gly Ala Ser Glu Met Ile Ile Met His Leu Asn Gly Pro Val

get gae aag ete cag tat gte gte aca eea etg ttg ett eet gae ace

Ala Asp Lys Leu Gln Tyr Val Val Thr Pro Leu Leu Pro Asp Thr

90

105

100

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gac cca att gga cgc atc gca caa cga cgc atc act gat gct ttg ta Asp Pro Ile Gly Arg Ile Ala Gln Arg Arg Ile Thr Asp Ala Leu Ty 135 140 145	c 547
gac cgt gat gac gca cta gaa gat cgt gtt gag aac tat cac cca gg Asp Arg Asp Asp Ala Leu Glu Asp Arg Val Glu Asn Tyr His Pro Gl 150 155 160 16	У
gat acc gac atg acg tgg gcg cgc ctt acc cag tgg cgg gga ctt gt Asp Thr Asp Met Thr Trp Ala Arg Leu Thr Gln Trp Arg Gly Leu Va 170 175 180	t 643 1
gcc tcc tca ttg gat cac cca cca cac agc gaa atc act tcc gtg aga Ala Ser Ser Leu Asp His Pro Pro His Ser Glu Ile Thr Ser Val Arc 185 190 195	g 691 g
ctg acc ggt gca agc ggc agt acc tcg gtg gat ttg gct gca ggc tgc Leu Thr Gly Ala Ser Gly Ser Thr Ser Val Asp Leu Ala Ala Gly Trp 200 205 210	p
ttg gcg cgg agg ctg aaa gtg cct gtg atc cgc gag gtg aca gat gc Leu Ala Arg Arg Leu Lys Val Pro Val Ile Arg Glu Val Thr Asp Ala 215 220 225	a
ccc acc gtg cca acc gat gag ttt ggt act cca ctg ctg gct atc cag Pro Thr Val Pro Thr Asp Glu Phe Gly Thr Pro Leu Leu Ala Ile Glr 230 235 240 245	i 5
cgc ctg gag atc gtt cgc acc acc ggc tcg atc atc acc atc tat Arg Leu Glu Ile Val Arg Thr Thr Gly Ser Ile Ile Ile Thr Ile Tyr 250 255 260	•
gac gct cat acc ctt cag gta gag atg ccg gaa tcc ggc aat gcc cca Asp Ala His Thr Leu Gln Val Glu Met Pro Glu Ser Gly Asn Ala Pro 265 270 275	
tcg ctg gtg gct att ggt cgt cga agt gag tcc gac tgc ttg tct gag Ser Leu Val Ala Ile Gly Arg Arg Ser Glu Ser Asp Cys Leu Ser Glu 280 285 290	
gag ctt cgc cac atg gat cca gat ttg ggc tac cag cac gca cta tcc Glu Leu Arg His Met Asp Pro Asp Leu Gly Tyr Gln His Ala Leu Ser 295 300 305	
ggc ttg tcc agc gtc aag ctg gaa acc gtc taaggagaaa tacaacacta Gly Leu Ser Ser Val Lys Leu Glu Thr Val 310 315	1077

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tgg

<211> 319

<212> PRT

<213> Corynebacterium glutamicum

<400> 80

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Leu Thr Arg Leu Arg Glu Ser Gly Thr Gln Val Thr Thr Gly Arg Val
20 25 30

Leu Thr Leu Ile Val Val Thr Asp Ser Glu Ser Asp Val Ala Ala Val 35 40 45

Thr Glu Ser Thr Asn Glu Ala Ser Arg Glu His Pro Ser Arg Val Ile 50 55 60

Ile Leu Val Val Gly Asp Lys Thr Ala Glu Asn Lys Val Asp Ala Glu 65 70 75 80

Val Arg Ile Gly Gly Asp Ala Gly Ala Ser Glu Met Ile Ile Met His 85 90 95

Leu Asn Gly Pro Val Ala Asp Lys Leu Gln Tyr Val Val Thr Pro Leu
100 105 110

Leu Leu Pro Asp Thr Pro Ile Val Ala Trp Trp Pro Gly Glu Ser Pro
115 120 125

Lys Asn Pro Ser Gln Asp Pro Ile Gly Arg Ile Ala Gln Arg Arg Ile 130 135 140

Thr Asp Ala Leu Tyr Asp Arg Asp Asp Ala Leu Glu Asp Arg Val Glu 145 150 155 160

Asn Tyr His Pro Gly Asp Thr Asp Met Thr Trp Ala Arg Leu Thr Gln
165 170 175

Trp Arg Gly Leu Val Ala Ser Ser Leu Asp His Pro Pro His Ser Glu 180 185 190

Ile Thr Ser Val Arg Leu Thr Gly Ala Ser Gly Ser Thr Ser Val Asp 195 200 205

Leu Ala Ala Gly Trp Leu Ala Arg Arg Leu Lys Val Pro Val Ile Arg 210 215 220

Glu Val Thr Asp Ala Pro Thr Val Pro Thr Asp Glu Phe Gly Thr Pro 225 230 235 240

Leu Leu Ala Ile Gln Arg Leu Glu Ile Val Arg Thr Thr Gly Ser Ile 245 250 255

Ile Ile Thr Ile Tyr Asp Ala His Thr Leu Gln Val Glu Met Pro Glu 260 265 270

Ser Gly Asn Ala Pro Ser Leu Val Ala Ile Gly Arg Arg Ser Glu Ser

275

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Phe Ile Ala Pro Asn Asp Gly Ser Ala Asp Leu Phe Val His Tyr Ser 25

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211 Asp Gly Ser Ala Asp Leu Phe Val His Tyr Ser Glu Ile Gln Gly Ser ggt ttc cgt aat ctt gag gaa aac cag cca gtt gaa ttt gag gtc ggc 259 Gly Phe Arg Asn Leu Glu Glu Asn Gln Pro Val Glu Phe Glu Val Gly 40 -

gag ggc gcc aag ggc cca cag gct cag cag gtt cgt gct ctc 301 Glu Gly Ala Lys Gly Pro Gln Ala Gln Gln Val Arg Ala Leu 60

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Glu Phe Glu Val Gly Glu Gly Ala Lys Gly Pro Gln Ala Gln Gln Val 50 55 60

Arg Ala Leu 65

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Val Pro Val Gly Thr
1 5

gtg aag tgg tac gac gcg gag cgt ggt ttc ggc ttt gtc tcc aat cca 163 Val Lys Trp Tyr Asp Ala Glu Arg Gly Phe Gly Phe Val Ser Asn Pro

ggt ggt gaa gat tgc ttc gta ggt aag caa gta ctt ccc aag gga gtc 211 Gly Gly Glu Asp Cys Phe Val Gly Lys Gln Val Leu Pro Lys Gly Val 25 30 35

acc gaa ttg cac aag gga cag cga atc gat ttt gac ttc gcc gca ggc 259
Thr Glu Leu His Lys Gly Gln Arg Ile Asp Phe Asp Phe Ala Ala Gly
40 45 50

cgt aag ggc cct caa gca ctt cga ata aag att ctt gaa act cca cgc 307 Arg Lys Gly Pro Gln Ala Leu Arg Ile Lys Ile Leu Glu Thr Pro Arg 55 60 65

agg cgt cca cag cac aaa tac aag cca gaa gag ctc aac gga atg atc 355 Arg Arg Pro Gln His Lys Tyr Lys Pro Glu Glu Leu Asn Gly Met Ile 70 75 80 85

tct gac ctc atc acg ctt cta gaa agt gga gtg caa cca ggc ctt gcc 403 Ser Asp Leu Ile Thr Leu Leu Glu Ser Gly Val Gln Pro Gly Leu Ala 90 95 100

aaa ggg caa tac ccg gag cac aaa gct gga gcg cag gta gca gaa att 451 Lys Gly Gln Tyr Pro Glu His Lys Ala Gly Ala Gln Val Ala Glu Ile 105 110 115

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ccg

504

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Leu Pro Lys Gly Val Thr Glu Leu His Lys Gly Gln Arg Ile Asp Phe 35 40 45

Asp Phe Ala Ala Gly Arg Lys Gly Pro Gln Ala Leu Arg Ile Lys Ile 50 55 60

Leu Glu Thr Pro Arg Arg Pro Gln His Lys Tyr Lys Pro Glu Glu 65 70 75 80

Leu Asn Gly Met Ile Ser Asp Leu Ile Thr Leu Leu Glu Ser Gly Val
85 90 95

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Met Ala Gln Gly Thr

1 5

gtt aag tgg ttc aac cca gag aag ggc ttc ggc ttc atc gct cct tcc 163 Val Lys Trp Phe Asn Pro Glu Lys Gly Phe Gly Phe Ile Ala Pro Ser 10 15 20

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ggc ttc cgt acc ctc gag gag aac cag ctc gtc gag ttc gaa atc ggc Gly Phe Arg Thr Leu Glu Glu Asn Gln Leu Val Glu Phe Glu Ile Gly 40 45 50	259
gag ggc gct aag ggc ctt cag gct cag gct gtt cgt gca atc Glu Gly Ala Lys Gly Leu Gln Ala Gln Ala Val Arg Ala Ile 55 60 65	301
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Phe Ile Ala Pro Ser Asp Gly Ser Ala Asp Val Phe Val His Tyr Ser 20 25 30	٠
Glu Ile Glu Gly Asn Gly Phe Arg Thr Leu Glu Glu Asn Gln Leu Val 35 40 45	
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ccg aac ctg caa act ctc gca ctc ttt gtg gcg att gtg gaa gag ggg Pro Asn Leu Gln Thr Leu Ala Leu Phe Val Ala Ile Val Glu Gly	163

10

				a Gl					L GI) Asr	gcc Ala	211
			a Il					ı Ala					Glu		ı ttg ı Leu	259
		Hi:			agga gGly		His					Gly			ctt Leu	307
	. Glu				gat JAsp 75	Leu					. Glr					355
					cga Arg					Leu					Gly	403
				Ile	gcc Ala									Ala		451
			Arg		cct Pro											499
		Gln			gaa Glu											547
					cat His 155											595
					att Ile											643
					atc Ile											691
					ggc Gly	Ser										739
					atg Met					Gln						787
gct Ala 230	gcg Ala	gta Val	cgt Arg	Val	gtt (Val \ 235	gtt (Val (gaa Glu .	gca Ala	Gly	gca Ala 240	ggt Gly	cct Pro	gca Ala	Val	ctt Leu 245	835

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Ile	Val	Glu	Glu 20	_	Ser	Leu	Gly	Ala 25	_	Ala	Arg	Lys	Val 30	Gly	Met	
Ala	Gln	Pro 35	Asn	Ala	Ser	Arg	Ala 40		Ala	Glu	Leu	Glu 45	Ala	Asp	Met	
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Ala 65	_	Leu	Ala	Leu	Val 70	Glu	His	Ser	Arg	Asp 75	Leu	Leu	Gln	Ser	Val 80	
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Val	Ser 130	Val	Met	Asn	Ser	Ser 135	Gln	Val	Ile	Glu	Ala 140	Val	Gln	Lys	Gly	
His 145	Leu	Gln	Leu	Gly	Phe 150	Ile	Glu	Thr	Pro	His 155	Val	Pro	Val	Arg	Leu 160	
His	Ala	Arg	Val	Val 165	Gln	Glu	Asp	Lys	Leu 170	Ile	Val	Val	Ile	Ser 175	Pro	

Ser Glu Thr	Pro Leu	Ile '	Val.	Arg	Glu	Val	Gly	Ser	Gly	Thr	Arg	Glu
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Ala Leu Gln Glu Leu Leu Ala Asp Tyr Asp Met Ala Glu Pro Ile Gln 210 215 220

Val Leu Asn Ser Asn Ala Ala Val Arg Val Val Val Glu Ala Gly Ala 225 230 235 240

Gly Pro Ala Val Leu Gly Glu Leu Ala Leu Arg Asp His Leu Ala Leu 245 250 255

Gly Arg Leu Leu Ser Val Pro Phe Glu Gly Ser Gly Val Thr Arg Pro 260 270

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atc gat gaa ggc ttc atg gaa cca gag gct ctc gtt gga gcc acc cca 144
Ile Asp Glu Gly Phe Met Glu Pro Glu Ala Leu Val Gly Ala Thr Pro
35 40 45

gaa gag gtg aaa cag tgg gcg gaa gaa tta cgc gcg gaa att aaa gaa 192 Glu Glu Val Lys Gln Trp Ala Glu Glu Leu Arg Ala Glu Ile Lys Glu 50 55 60

gtt act ggc tta ccc tcc tcg gtt ggt gct ggc tcc ggt aag cag atc 240 Val Thr Gly Leu Pro Ser Ser Val Gly Ala Gly Ser Gly Lys Gln Ile 65 70 75 80

gcc aaa att ggt tca ggc gaa gca aag cca gat ggt gtg ttt gtc gtg 288

Al	a Ly	s II	.e Gl	• _	er Gl	y, Gl	u Al	a Ly	s Pr 9		p Ģl	y Va.	1 Ph	e Va	l Val	
				rs Gl					u As					1 G1	c gca y Ala	336
			y Va					r Gl					a Se		g ggg t Gly	384
		u Th					ı Ala					n Lys			a gaa l Glu	432
	e Se					: Ile					ı Trp				c cga Arg 160	480
gga Gl	ato 7 Ile	e As _l	c ga p As	c cg p Are 16	g Pro	gtg Val	gaa Glu	cco Pro	e ego Arg 170	Ala	gaa Glu	gca Ala	aaa Lys	caç Glr 175	g atc n Ile	528
				s Thi	tat Tyr				Leu					Glr	gta Val	576
gat Asp	gct Ala	gco Ala 195	ılle	atte Ile	cga Arg	tca Ser	gcc Ala 200	gaa Glu	ggc	gca Ala	cac His	cga Arg 205	Arg	cto Leu	ctc Leu	624
aaa Lys	gac Asp 210	Gly	cgc Arg	ggt Gly	gcc Ala	aga Arg 215	act Thr	gtc Val	agc Ser	gtg Val	aaa Lys 220	ctg Leu	cgg Arg	atg Met	gcc Ala	672
gac Asp 225	Phe	cgt Arg	att Ile	gag Glu	Ser 230	cgt Arg	tcc Ser	tac Tyr	acc Thr	ttg Leu 235	tcc Ser	tat Tyr	gcc Ala	acc Thr	gat Asp 240	720
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					atc Ile											816
gaa Glu	gaa Glu	tcc Ser 275	cgc Arg	caa Gln	gac Asp	Ile	ctc Leu 280	ttc Phe	ccg Pro	gaa Glu	ctt Leu	gac Asp 285	caa Gln	caa Gln	atc Ile	864
atc Ile	gta Val 290	cca Pro	cca Pro	gca Ala	ccc Pro	gac Asp 295	acc Thr	gat Asp	tat Tyr	gag Glu	gta Val 300	ggc Gly	gtg Val	caa Gln	tcc Ser	912
tct Ser	tct Ser	agt Ser	tcc Ser	gaa Glu	agt Ser	act of	caa Gln	gtt Val	gaa Glu	gcg Ala	ccg Pro	caa Gln	gat Asp	gtc Val	gcg Ala	960

305 310 315 320 ttg agt atg tgg tgc gca acg caa gat gtc tac cac cca gaa tat ggc 1008 Leu Ser Met Trp Cys Ala Thr Gln Asp Val Tyr His Pro Glu Tyr Gly 325 cac ggt tgg gta caa ggt gcc ggt cac ggt gtt gta tca gta cgt ttt 1056 His Gly Trp Val Gln Gly Ala Gly His Gly Val Val Ser Val Arg Phe 350 gaa acc cgc agc acc aca aaa ggg cga act aaa agt ttt tcc atg gat 1104 Glu Thr Arg Ser Thr Thr Lys Gly Arg Thr Lys Ser Phe Ser Met Asp 355 360 365 gac ecg gac etc ace ecg gea gac ect eta gat agt ttg gat tgg get 1152 Asp Pro Asp Leu Thr Pro Ala Asp Pro Leu Asp Ser Leu Asp Trp Ala 370 375 380 1201

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<213> Corynebacterium glutamicum

<400> 92

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Ile Asp Glu Gly Phe Met Glu Pro Glu Ala Leu Val Gly Ala Thr Pro 35 40 45

Glu Glu Val Lys Gln Trp Ala Glu Glu Leu Arg Ala Glu Ile Lys Glu 50 55 60

Val Thr Gly Leu Pro Ser Ser Val Gly Ala Gly Ser Gly Lys Gln Ile 65 70 75 80

Ala Lys Ile Gly Ser Gly Glu Ala Lys Pro Asp Gly Val Phe Val Val 85 90 95

Pro Val Asp Lys Gln His Asp Leu Leu Asp Pro Leu Pro Val Gly Ala 100 105 110

Leu Trp Gly Val Gly Pro Val Thr Gly Ser Lys Leu Ala Ser Met Gly
115 120 125

Val Glu Thr Ile Gly Asp Leu Ala Ala Leu Thr Gln Lys Glu Val Glu 130 135 140 Ile Ser Leu Gly Ala Thr Ile Gly Ile Ser Leu Trp Asn Leu Ala Arg 145 150 155 160

Gly Ile Asp Asp Arg Pro Val Glu Pro Arg Ala Glu Ala Lys Gln Ile 165 170 175

Ser Gln Glu His Thr Tyr Glu Lys Asp Leu Leu Thr Arg Gln Gln Val 180 185 190

Asp Ala Ala Ile Ile Arg Ser Ala Glu Gly Ala His Arg Arg Leu Leu 195 200 205

Lys Asp Gly Arg Gly Ala Arg Thr Val Ser Val Lys Leu Arg Met Ala 210 215 220

Asp Phe Arg Ile Glu Ser Arg Ser Tyr Thr Leu Ser Tyr Ala Thr Asp 225 230 235 240

Asp Tyr Ala Thr Leu Glu Ala Thr Ala Phe Arg Leu Ala Arg Tyr Pro 245 250 255

Gly Glu Val Gly Pro Ile Arg Leu Val Gly Val Ser Phe Ser Gly Leu 260 265 270

Glu Glu Ser Arg Gln Asp Ile Leu Phe Pro Glu Leu Asp Gln Gln Ile 275 280 285

Ile Val Pro Pro Ala Pro Asp Thr Asp Tyr Glu Val Gly Val Gln Ser 290 295 300

Ser Ser Ser Ser Glu Ser Thr Gln Val Glu Ala Pro Gln Asp Val Ala 305 310 315 320

Leu Ser Met Trp Cys Ala Thr Gln Asp Val Tyr His Pro Glu Tyr Gly 325 330 335

His Gly Trp Val Gln Gly Ala Gly His Gly Val Val Ser Val Arg Phe 340 345 350

Glu Thr Arg Ser Thr Thr Lys Gly Arg Thr Lys Ser Phe Ser Met Asp 355 360 365

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at Il	c gc e Ala	g tad a Tyn	c acc	agt Ser 10	Glu	a gca a Ala	teu	tca Ser	aco Thi	Gly	c agt y Ser	ggc Gly	cgg Arg	ctg Leu 20	Gly	163
ca Hi	t gtg s Val	g cgc L Arg	tcc Ser 25	Thr	gat Asp	ggt Gly	gcg Ala	cto Leu 30	Glu	ttt Phe	gaa Glu	atg Met	aca Thr 35	Pro	cca Pro	211
aa Ly	g gct s Ala	ttg Leu 40	Gly	gga Gly	tcc Ser	ggt Gly	gaa Glu 45	Gly	acc	aat Asn	cca Pro	gaa Glu 50	cag Gln	ctg Leu	ttc Phe	259
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arg Arg 70	c agc g Ser)	cgc Arg	aag Lys	atc Ile	act Thr 75	ctt Leu	gaa Glu	gac Asp	aca Thr	gcg Ala 80	gtt Val	ggt Gly	gcc Ala	cga Arg	gtt Val 85	355
ago Ser	atc : Ile	Gly ggg	cca Pro	aac Asn 90	ggc Gly	gct Ala	ggt Gly	gga Gly	ttt Phe 95	gag Glu	att Ile	gcc Ala	gta Val	gaa Glu 100	ctc Leu	403
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Pr	50 50	ı Gln	Leu	Phe	Ala	Val 55	Gly	Tyr	Ala	Ala	Cys 60		His	Ser	Ala	
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Va]	l Gly	Ala	Arg	Val 85	Ser	Ile	Gly	Pro	Asn 90	Gly	Ala	Gly	Gly	Phe 95		
Ile	e Ala	Val	Glu 100	Leu	Glu	Val	Ser	Ile 105	Pro	Gln	Leu	Pro	Gln 110	Ala	Glu	
Ala	Gln	Glu 115	Leu	Ala	Asp	Ala	Ala 120	His	Gln	Val	Cys	Pro 125	Tyr	Ser	Asn	
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Ala 145																
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gaag	gtat	ta a	tactt	ctt	aaq	ggto	egga	ggat	tttt		atg Met 1				aca Thr 5	115
acg Thr	cca Pro	caa q Gln <i>F</i>	A qe	gt t rg T 10	at a 'yr T	cc g	ac g sp 0	gaa t Slu 1	ac (Tyr (ggc Gly	atc (gaa (Glu)	ege Arg	gtc Val 20	aac Asn	163
aag Lys	gat Asp	gaa c Glu F	cc g ro G 25	gc c ly L	tg g eu V	tg g al A	ac a sp L	aa c ys I 30	etc o Leu A	egg (gac a Asp 1	aag d Lys i	cac d His 1 35	gac Asp	tgg Trp	211
ttt Phe	gat (Asp)	cat c His L 40	tc a eu M	tg c et A	gc a rg M	et A	at g sn G 45	aa c lu A	gt t	tc o	ggc (Sly <i>P</i>	jca a Ala I 50	aaa d Lys (ggt Gly	ggc Gly	259

		n Le					e Thi					l Lei			c ttc e Phe	307
	o Ile					l Phe					y Val				c gga a Gly 85	355
					ı Thi					Arg					t tta a Leu)	403
				e Gl					G1 _y					Ala	g att	451
			g Gly					Ile					Ala		tgg Trp	499
Ser	Gly 135	Leu	ı Gly	/ Trp	Met	Ala 140	Asn	Leu	Arg	Phe	Gly 145	Val	Ser	Arg		547
Trp 150	Ala	Ile	Asp	cca Pro	Thr 155	Glu	Gly	Asn	Phe	11e 160	Gln	Lys	Lys	Leu	Thr 165	595
Asp	Leu	Val	Ala	ctg Leu 170	Ile	Val	Leu	Leu	Leu 175	Ala	Met	Gly	Val	Ala 180	Phe	643
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Phe	Val	Gly 200	Leu	ggg Gly	Glu	Ile	Pro 205	ĞÎy	Ile	Ser	Tyr	Ile 210	Thr	Trp	Val	739
Val	Ala 215	Ala	Leu	gtt Val	Gly	Val 220	Leu	Ala	Asn	Phe	Leu 225	Val	Phe	Met	Trp	787
Leu 230	Ile	Phe	Ser	ctg Leu	Pro 235	Arg	Thr	Lys	Val	Pro 240	Met	Lys	Pro	Gly	Leu 245	835
Gln	Ala	Ala	Leu	ctt Leu 250	Gly .	Ala	Ile	Gly	Phe 255	Glu	Val	Val	Lys	Gln 260	Val	883
gga Gly	tcg Ser	ctg Leu	ttg Leu 265	gct Ala	tca (Ser i	aat Asn	Ala :	ttg Leu : 270	agt Ser	aac Asn	ccc Pro	Ala	ggt Gly 275	gca Ala	gca Ala	931

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atc ctc atg tat tgc tct gcg tgg gct gc Ile Leu Met Tyr Cys Ser Ala Trp Ala A 295 300		1027
cgt ctt gcg act gtt cca gca cca gag co Arg Leu Ala Thr Val Pro Ala Pro Glu Pr 310		1075
cat gaa att gat cca ggt gaa gaa gtc to His Glu Ile Asp Pro Gly Glu Glu Val Se 330	r Gln Ser Ala Arg Lys Val	1123
ggc att gga gtg gcc gtg ggt gcc gcg ac Gly Ile Gly Val Ala Val Gly Ala Ala Th 345 350		1171
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<400> 96		
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Asp Lys His Asp Trp Phe Asp His Leu Met 35 40	Arg Met Asn Glu Arg Phe	
Gly Ala Lys Gly Gly Asn Gln Leu Ser Ala 50 55	Gly Ile Thr Tyr Phe Ser 60	
Val Leu Ser Ile Phe Pro Ile Ala Met Leu 65 70	Val Phe Gly Ile Ala Gly 75 80	
Val Ile Leu Ala Gly Asn Pro Glu Val Leu 85 90	Thr Asp Ile Gln Asn Arg 95	
Ile Asn Asp Ala Leu Glu Gly Glu Ile Gly	Asn Thr Val Asn Gly Ile	

Ile Asp Ser Ala Ile Ala Gln Arg Gly Ala Val Leu Gly Ile Gly Gly

Val Thr Ala Leu Trp Ser Gly Leu Gly Trp Met Ala Asn Leu Arg Phe

Gly Val Ser Arg Met Trp Ala Ile Asp Pro Thr Glu Gly Asn Phe Ile
145 150 155 160

Gly Lyg Lyg Ley Thr Asp Ley Val Ala Ley Ile Val Ley Ley Ala

Gln-Lys Lys Leu Thr Asp Leu Val Ala Leu Ile Val Leu Leu Leu Ala 165 170 175

Met Gly Val Ala Phe Gly Ile Thr Ala Leu Gly Ala Ser Gly Leu Thr 180 185 190

Lys Asn Leu Leu Asp Phe Val Gly Leu Gly Glu Ile Pro Gly Ile Ser 195 200 205

Tyr Ile Thr Trp Val Val Ala Ala Leu Val Gly Val Leu Ala Asn Phe 210 225

Leu Val Phe Met Trp Leu Ile Phe Ser Leu Pro Arg Thr Lys Val Pro 225 235 240

Met Lys Pro Gly Leu Gln Ala Ala Leu Leu Gly Ala Ile Gly Phe Glu 245 250 255

Val Val Lys Gln Val Gly Ser Leu Leu Ala Ser Asn Ala Leu Ser Asn 260 265 270

Pro Ala Gly Ala Ala Phe Gly Pro Ile Ile Gly Ile Met Val Val Leu 275 280 285

Tyr Leu Ile Trp Arg Ile Leu Met Tyr Cys Ser Ala Trp Ala Ala Thr 290 295 300

Ser Glu Glu Ala Leu Arg Leu Ala Thr Val Pro Ala Pro Glu Pro Ala 305 310 315 320

Ile Ile Arg Val Arg His Glu Ile Asp Pro Gly Glu Glu Val Ser Gln 325 330 335

Ser Ala Arg Lys Val Gly Ile Gly Val Ala Val Gly Ala Ala Thr Ala 340 345

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cca gcg ccc gag aat ctc ctg gac gcc gag aga att cag atg atc aag Pro Ala Pro Glu Asn Leu Leu Asp Ala Glu Arg Ile Gln Met Ile Lys 10 15 20	163
aac ttc cgc aac gaa tta acg ggg ttc atg ctc aac tac caa ttt ggc Asn Phe Arg Asn Glu Leu Thr Gly Phe Met Leu Asn Tyr Gln Phe Gly 25 30 35	211
att gat gag atc ctg acc aag atc aac atc ctg aaa act gaa ttc agc Ile Asp Glu Ile Leu Thr Lys Ile Asn Ile Leu Lys Thr Glu Phe Ser 40 45 50	259
cag ctg cac gaa tac gca cct atc gag cac gta tct tca cga ttg aag Gln Leu His Glu Tyr Ala Pro Ile Glu His Val Ser Ser Arg Leu Lys 55 60 65	307
aca cca gaa agc atc gtc aaa aag gtc atc cga aaa gga gac gag ctc Thr Pro Glu Ser Ile Val Lys Lys Val Ile Arg Lys Gly Asp Glu Leu 70 75 80 85	355
tcc ctc gca gct atc aaa gac aca gtg ttt gat atc gca ggc att cga Ser Leu Ala Ala Ile Lys Asp Thr Val Phe Asp Ile Ala Gly Ile Arg 90 95 100	403
atc gtc tgc agt ttc ctc aaa gat gcc tac gca atc gcc gat atg ctg Ile Val Cys Ser Phe Leu Lys Asp Ala Tyr Ala Ile Ala Asp Met Leu 105 110 115	451
acc aac caa aaa gac gtc acg gtc atc gag gcc aaa gac tac atc gct Thr Asn Gln Lys Asp Val Thr Val Ile Glu Ala Lys Asp Tyr Ile Ala 120 125 130	499
aac cca aag ccg aac ggc tac aag agt ttg cac ctt atc ctc caa gtg Asn Pro Lys Pro Asn Gly Tyr Lys Ser Leu His Leu Ile Leu Gln Val 135 140 145	547
cct gtc ttc ctg tct aac tcc gtg gaa aag gtc aat gtt gaa gtc cag Pro Val Phe Leu Ser Asn Ser Val Glu Lys Val Asn Val Glu Val Gln 150 155 160 165	595
atc cgc acc att gcc atg gac ttc tgg gca agc ctc gag cac aaa atc Ile Arg Thr Ile Ala Met Asp Phe Trp Ala Ser Leu Glu His Lys Ile 170 175 180	643
tac tac aaa ttt gaa caa gaa gtt cct cag tca atc ctt gat gag ctc Tyr Tyr Lys Phe Glu Gln Glu Val Pro Gln Ser Ile Leu Asp Glu Leu 185 190 195	691
agt gaa gat gga aag aat cca cgg gga agt gaa gtc act taaacctcca Ser Glu Asp Gly Lys Asn Pro Arg Gly Ser Glu Val Thr 200 205 210	740
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Asn Tyr Gln Phe Gly Ile Asp Glu Ile Leu Thr Lys Ile Asn Ile Leu

Lys Thr Glu Phe Ser Gln Leu His Glu Tyr Ala Pro Ile Glu His Val

Ser Ser Arg Leu Lys Thr Pro Glu Ser Ile Val Lys Lys Val Ile Arg

Lys Gly Asp Glu Leu Ser Leu Ala Ala Ile Lys Asp Thr Val Phe Asp

Ile Ala Gly Ile Arg Ile Val Cys Ser Phe Leu Lys Asp Ala Tyr Ala

Ile Ala Asp Met Leu Thr Asn Gln Lys Asp Val Thr Val Ile Glu Ala

Lys Asp Tyr Ile Ala Asn Pro Lys Pro Asn Gly Tyr Lys Ser Leu His

Leu Ile Leu Gln Val Pro Val Phe Leu Ser Asn Ser Val Glu Lys Val

Asn Val Glu Val Gln Ile Arg Thr Ile Ala Met Asp Phe Trp Ala Ser

Leu Glu His Lys Ile Tyr Tyr Lys Phe Glu Gln Glu Val Pro Gln Ser

Ile Leu Asp Glu Leu Ser Glu Asp Gly Lys Asn Pro Arg Gly Ser Glu 200

Val Thr 210

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- atc agc ccc gaa acc aaa acc gga aag aag atc ctg ctt gca gcc cct 163
 Ile Ser Pro Glu Thr Lys Thr Gly Lys Lys Ile Leu Leu Ala Ala Pro
 10 15 20
- cgc gga tac tgt gcc ggc gta gac cgt gca gtg gaa acc gtc gag cgc 211 Arg Gly Tyr Cys Ala Gly Val Asp Arg Ala Val Glu Thr Val Glu Arg 25 30 35
- gcg ctc gag gaa tac ggc gcc cca att tat gtc cgt aaa gaa atc gtg 259
 Ala Leu Glu Glu Tyr Gly Ala Pro Ile Tyr Val Arg Lys Glu Ile Val
 40 50
- cac aac cgt tac gtt gtg gac acc ctg gca gaa aag ggc gcg att ttt 307 His Asn Arg Tyr Val Val Asp Thr Leu Ala Glu Lys Gly Ala Ile Phe
- gtc aac gaa gca tct gaa gca cca gaa ggt gcc aac atg gtg ttc tct 355
 Val Asn Glu Ala Ser Glu Ala Pro Glu Gly Ala Asn Met Val Phe Ser
 70 75 80 85
- gca cac ggc gtg agc cca atg gtc cac gaa gaa gct gca gct aaa aac 403 Ala His Gly Val Ser Pro Met Val His Glu Glu Ala Ala Ala Lys Asn 90 95 100
- atc aag gct att gac gcg gcc tgc ccg ctg gtc acc aaa gtg cac aag 451
 Ile Lys Ala Ile Asp Ala Ala Cys Pro Leu Val Thr Lys Val His Lys
 105 110 115
- gaa gtc cag cgc ttt gat aag cag gga ttc cac att ctc ttc atc ggt 499
 Glu Val Gln Arg Phe Asp Lys Gln Gly Phe His Ile Leu Phe Ile Gly
 120 125 130
- cac gaa ggc cat gaa gaa gta gag ggc acc atg ggt cat tcc gtt gag 547 His Glu Gly His Glu Glu Val Glu Gly Thr Met Gly His Ser Val Glu 135 140 145
- aaa acc cac ctg gtt gac ggc gtt gct ggc att gcc acc ctg cct gaa 595 Lys Thr His Leu Val Asp Gly Val Ala Gly Ile Ala Thr Leu Pro Glu
- ttc tta aac gat gaa cca aac ctg atc tgg ctg tct cag acc acg ctt
 Phe Leu Asn Asp Glu Pro Asn Leu Ile Trp Leu Ser Gln Thr Thr Leu
 170 175 180
- tct gtg gac gag acc atg gag atc gtc cgc gag ctg aag gtg aag ttc 691 Ser Val Asp Glu Thr Met Glu Ile Val Arg Glu Leu Lys Val Lys Phe

185

190

cct cag ctg cag gat cca ccg tca gat gat att tgc tac gcc acg cag 739 Pro Gln Leu Gln Asp Pro Pro Ser Asp Asp Ile Cys Tyr Ala Thr Gln 200 205 aac ege cag gtt gee gte aag get ate get gag ege tge gag etg atg 787 Asn Arg Gln Val Ala Val Lys Ala Ile Ala Glu Arg Cys Glu Leu Met 215 220 att gtg gtc ggt tcc cgc aac tcc tcc aac tcg gtt cgt ctg gtt gag 835 Ile Val Val Gly Ser Arg Asn Ser Ser Asn Ser Val Arg Leu Val Glu gto got aag caa aac ggt goo gat aac goo tac otg gtg gat tac goo 883 Val Ala Lys Gln Asn Gly Ala Asp Asn Ala Tyr Leu Val Asp Tyr Ala 250 260 cgc gaa atc gac cca gca tgg ttc gaa ggc gta gag acc atc ggt atc 931 Arg Glu Ile Asp Pro Ala Trp Phe Glu Gly Val Glu Thr Ile Gly Ile 265 270 275 tcc tcc ggc gct tcc gtg cct gag atc ctc gtc cag ggc gtc att gag Ser Ser Gly Ala Ser Val Pro Glu Ile Leu Val Gln Gly Val Ile Glu 280 285 290 cgc ctg gct gag ttc ggc tac gac gtc gag gaa gtc acc tcc gcc 1027 Arg Leu Ala Glu Phe Gly Tyr Asp Asp Val Glu Glu Val Thr Ser Ala 295 300 get gag aag att gtt tte geg etg eet ege gtg etg ege eac aag aat Ala Glu Lys Ile Val Phe Ala Leu Pro Arg Val Leu Arg His Lys Asn 310 315 320 taattgcaag aatgaaaaat ccc 1098 <210> 100 <211> 325 <212> PRT <213> Corynebacterium glutamicum <400> 100

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Arg Lys Glu Ile Val His Asn Arg Tyr Val Val Asp Thr Leu Ala Glu

Lys Gly Ala Ile Phe Val Asn Glu Ala Ser Glu Ala Pro Glu Gly Ala 65 70

Asn Met Val Phe Ser Ala His Gly Val Ser Pro Met Val His Glu Glu 85 90 95

Ala Ala Lys Asn Ile Lys Ala Ile Asp Ala Ala Cys Pro Leu Val 100 105 110

Thr Lys Val His Lys Glu Val Gln Arg Phe Asp Lys Gln Gly Phe His 115 120 125

Ile Leu Phe Ile Gly His Glu Gly His Glu Glu Val Glu Gly Thr Met 130 135 140

Gly His Ser Val Glu Lys Thr His Leu Val Asp Gly Val Ala Gly Ile 145 150 155 160

Ala Thr Leu Pro Glu Phe Leu Asn Asp Glu Pro Asn Leu Ile Trp Leu 165 170 175

Ser Gln Thr Thr Leu Ser Val Asp Glu Thr Met Glu Ile Val Arg Glu 180 185 190

Leu Lys Val Lys Phe Pro Gln Leu Gln Asp Pro Pro Ser Asp Asp Ile 195 200 205

Cys Tyr Ala Thr Gln Asn Arg Gln Val Ala Val Lys Ala Ile Ala Glu 210 215 220

Arg Cys Glu Leu Met Ile Val Val Gly Ser Arg Asn Ser Ser Asn Ser 225 230 235 240

Val Arg Leu Val Glu Val Ala Lys Gln Asn Gly Ala Asp Asn Ala Tyr 245 250 255

Leu Val Asp Tyr Ala Arg Glu Ile Asp Pro Ala Trp Phe Glu Gly Val 260 265 270

Glu Thr Ile Gly Ile Ser Ser Gly Ala Ser Val Pro Glu Ile Leu Val 275 280 285

Gln Gly Val Ile Glu Arg Leu Ala Glu Phe Gly Tyr Asp Asp Val Glu 290 295 300

Glu Val Thr Ser Ala Ala Glu Lys Ile Val Phe Ala Leu Pro Arg Val 305 310 315 320

Leu Arg His Lys Asn

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<211> 1131

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														•		
								Arg					Leu	gta Val		739
		Leu					Thr							ccc Pro		7 87
														ctc Leu		835
										Āla				gat Asp 260		883
														ggc Gly		93,1
														aaa Lys		979
									_		_		-	gcg Ala		1027
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cca															_	1131
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Arg Gly Asp Ile Thr Asn Pro Asp Ser Ile Glu Val Ala Val Ile His 50 55 60

Thr Glu Glu Phe Thr Arg Pro Thr Leu Ala Ala Gly Ala Val Leu Trp

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Arc 65		o Hi	s Ty	r Ası	Asp 70		Se ₁	. Lei	ı Ala	A Lys 75		/ Lys	Val	. Asp	Pro 80
Gl	/ Gli	ı Se:	rIl	e Pro		Thi	Ala	a Ala	Arg 90		ı Ile	Leu	Glu	Glu 95	Thr
Gly	/ Tyi	c Ası	100		, Leu	ı Gly	/ Lys	105		e Gly	Lys	Val	Thr 110		Pro
Val	. Lev	1 Asp 115		g Thr	Lys	. Val	Val		Туг	Trp	Thr	Ala 125		Val	Leu
Gly	Gly 130		ı Phe	e Val	Pro	Asn 135		Glu	Val	Asp	Glu 140	Ile	Arg	Trp	Leu
Ser 145		Asp	Glu	ı Ala	Cys 150		Leu	Leu	Ser	Tyr 155	Gln	Val	Asp	Thr	Glu 160
Val	Leu	Ala	Lys	Ala 165	Ala	Lys	Arg	Phe	Arg 170		Pro	Ser	Thr	Thr 175	Arg
Val	Leu	Tyr	Val 180	Arg	His	Ala	His	Ala 185	His	Gly	Arg	Gln	Thr 190	Trp	Gly
Gly	Asp	Asp 195		Lys	Arg	Pro	Leu 200	Asp	Lys	Lys	Gly	Arg 205	Arg	Gln	Ala
Glu	Met 210	Leu	Val	Pro	Met	Leu 215	Leu	Pro	Phe	Lys	Pro 220	Thr	Ala	Ile	Tyr
Ser 225	Ala	Val	Pro	Asp	Arg 230	Cys	Gln	Ala	Thr	Ala 235	Leu	Pro	Leu	Ala	Asp 240
Glu	Leu	Gly	Leu	Asp 245	Val	Ser	Val	Asn	Arg 250	Leu	Phe	Gly	Asp	Asp 255	Ala
Trp	Glu	Thr	Asp 260	Pro	Glu	Ala	Cys	Lys 265	Lys	Arg	Phe	Thr	Asp 270	Val	Val
Ala	Gln	Gly 275	Gly	Val	Pro	Met	Ile 280	Val	Gly	Gln	Gly	Asp 285	Ile	Ile	Pro
Glu	Met 290		Lys	Trp		Ser		Asn	Gly		Leu	Pro	Ile	Asp	Glu

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WO 01/00804

aag gaa aag gcg gag gga agg tcc acc cca agg tgattccgaa ccccaacccg 648

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aac 651

<210> 104

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<213> Corynebacterium glutamicum

<400> 104

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Ser Ala Gly Gly Leu Val Val Ser Gly Leu Ala Glu Ala Val Asn Ala 20 25 30

Asn Asn Glu Val Asp Leu Ser Lys Ile Tyr Val Ala Leu Ile Gly Arg 35 40 45

Leu Asp Arg Arg Gly Arg Leu Leu Trp Ser Met Pro Lys Gly His Val

Glu Pro Gly Glu Asp Lys Ala Ala Thr Ala Glu Arg Glu Val Trp Glu 65 70 75 80

Glu Thr Gly Ile His Gly Glu Val Phe Thr Glu Leu Gly Val Ile Asp 85 90 95

Tyr Trp Phe Val Ser Glu Gly Lys Arg Ile His Lys Thr Val His His 100 105 110

His Leu Leu Arg Tyr Val Asp Gly Asp Leu Asn Asp Glu Asp Pro Glu

Val Thr Glu Val Ala Trp Ile Pro Ala Asn Gln Leu Ile Glu His Leu 130 135 140

Ala Phe Ala Asp Glu Arg Lys Leu Ala Arg Gln Ala His Asp Leu Leu 145 150 155 160

Pro Glu Phe Ala Leu Lys Glu Lys Ala Glu Gly Arg Ser Thr Pro Arg 165 170 175

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gca Ala	atc Ile	gag Glu 35	cgc Arg	act Thr	cgt Arg	gtc Val	gct Ala 40	ttg Leu	gaa Glu	aac Asn	tac Tyr	gtt Val 45	gaa Glu	ctc Leu	atg Met	144
gaa Glu	acc Thr 50	cat His	ggg ggg	gta Val	gag Glu	gcc Ala 55	gta Val	cga Arg	atg Met	gtt Val	gcc Ala 60	acc Thr	tcc Ser	gca Ala	acc Thr	192
cgc Arg 65	gat Asp	gcg Ala	tcc Ser	aac Asn	cgc Arg 70	gat Asp	gaa Glu	ttc Phe	ttt Phe	tcg Ser 75	atg Met	acc Thr	cgc Arg	cag Gln	ctt Leu 80	240
ctg Leu	tcc Ser	aag Lys	atc Ile	cgt Arg 85	cct Pro	gga Gly	tac Tyr	caa Gln	gct Ala 90	gaa Glu	gta Val	att Ile	tcc Ser	ggc Gly 95	gaa Glu	288
gag Glu	gaa Glu	gct Ala	ctg Leu 100	ctg Leu	tcc Ser	ttc Phe	cga Arg	ggt Gly 105	gca Ala	atc Ile	gtt Val	gac Asp	ctg Leu 110	cct Pro	gaa Glu	336
gac Asp	caa Gln	ggt Gly 115	cct Pro	ttc Phe	tgt Cys	gtt Val	atc Ile 120	gac Asp	ctt Leu	ggc Gly	ggt Gly	gga Gly 125	tcc Ser	act Thr	gag Glu	384
ttc Phe	atc Ile 130	gtt Val	ggc Gly	acc Thr	tac Tyr	gac Asp 135	ggt Gly	gaa Glu	atc Ile	cta Leu	ggc Gly 140	tcc Ser	cac His	tca Ser	acc Thr	432
caa Gln 145	atg Met	gga Gly	tgc Cys	gtg Val	cgc Arg 150	ctg Leu	acc Thr	gaa Glu	cga Arg	atc Ile 155	atg Met	cgc Arg	agc Ser	gac Asp	cca Pro 160	480
ccc Pro		tgaa	accg	jaa g	ıtgga	aato	g co	c								509

<210> 106

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<213> Corynebacterium glutamicum

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			20					25					30		

Ala Ile Glu Arg Thr Arg Val Ala Leu Glu Asn Tyr Val Glu Leu Met 35 40 45

Glu Thr His Gly Val Glu Ala Val Arg Met Val Ala Thr Ser Ala Thr 50 55 60

Arg Asp Ala Ser Asn Arg Asp Glu Phe Phe Ser Met Thr Arg Gln Leu 65 70 75 80

Leu Ser Lys Ile Arg Pro Gly Tyr Gln Ala Glu Val Ile Ser Gly Glu 85 90 95

Glu Glu Ala Leu Leu Ser Phe Arg Gly Ala Ile Val Asp Leu Pro Glu 100 105 110

Asp Gln Gly Pro Phe Cys Val Ile Asp Leu Gly Gly Gly Ser Thr Glu 115 120 125

Phe Ile Val Gly Thr Tyr Asp Gly Glu Ile Leu Gly Ser His Ser Thr 130 135 140

Gln Met Gly Cys Val Arg Leu Thr Glu Arg Ile Met Arg Ser Asp Pro 145 150 155 160

Pro Asp

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Met Asn Thr Ala Ala
1 5

tgg gca cac cgc cac cac gta cgc aaa ggc ggt gga att ccg tat gtc 163
Trp Ala His Arg His His Val Arg Lys Gly Gly Gly Ile Pro Tyr Val
10 15 20

age cat ctt tat tea gtg atg tae ttg etg gee age gte act aat gat 211 Ser His Leu Tyr Ser Val Met Tyr Leu Leu Ala Ser Val Thr Asn Asp 25 30 35

gaa gat gtg ctc atc gcc ggg ctg ctc cac gac acc ctc gaa gac gta 259

	v	V O 01	/0080	4										\	PCT/IB00/00922
Glu	Asp	Val		Ile	Ala	Gly	Leu 45	His	Asp	Thr	Leu 50		Asp	Val	
		Glu					Gln				ttt Phe				
											tta Leu				
											gca Ala				403
											cat His				451
											tta Leu 130				499
											agc Ser				547
											aat Asn				595
						ctc Leu					tagg	rcgct	cg		641
gcgg	cgtc	ga t	aa												654

<210> 108

<211> 177

<212> PRT

<213> Corynebacterium glutamicum

<400> 108

Met Asn Thr Ala Ala Trp Ala His Arg His His Val Arg Lys Gly Gly 1 5 10 15

Gly Ile Pro Tyr Val Ser His Leu Tyr Ser Val Met Tyr Leu Leu Ala 20 25 30

Ser Val Thr Asn Asp Glu Asp Val Leu Ile Ala Gly Leu Leu His Asp 35 40 45

Thr Leu Glu Asp Val Pro Glu Glu Tyr Asn Ser Ala Gln Leu Glu Ala 50 55 60

Asp Phe Gly Pro Arg Val Arg Glu Leu Val Glu Glu Leu Thr Lys Gln

														_	
65					70					75					80
Pro	Leu	Lys	Ser	Trp 85		Ala	Arg	Ala	_	Ala	Tyr	Leu	Leu	His 95	Leu
Ser	Ala	Gly	Ala 100	Ser	Leu	Glu	Ala	Val 105	Leu	Ile	Ser	Thr	Ala 110	Asp	Lys
Leu	His	Asn 115	Leu	Met	Ser	Ile	Leu 120	Asp	Asp	Leu	Glu	Ile 125	His	Gly	Glu
Asp	Leu 130	Trp	Gln	Arg	Phe	Asn 135	Ala	Gly	Lys	Glu	Gln 140	Gln	Ile	Trp	Trp

Tyr Ser Glu Val Tyr Gln Ile Ser Leu Gln Arg Leu Gly Phe Asn Glu 145 150

Leu Asn Lys Gln Leu Gly Leu Cys Val Glu Lys Leu Leu Lys Gln Ser 170 175

Ala

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<400> 109

<223> RXS02497

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gattcacact ttgccaccct agaccgtcta acctttaggt gtg aga tta ggt gta Val Arg Leu Gly Val

tta gat gtg ggc agc aat act gtc cac cta gtt gca gta gac gcg cgt 163 Leu Asp Val Gly Ser Asn Thr Val His Leu Val Ala Val Asp Ala Arg 10

ccc ggt gga cac ccc acc ccg atg agc aat tgg cgt acc cca ctg cgc 211 Pro Gly Gly His Pro Thr Pro Met Ser Asn Trp Arg Thr Pro Leu Arg 25 30

ctt gtt gag ctt ctt gat gac tcc ggg gcg atc tcc gaa aag ggc atc 259 Leu Val Glu Leu Leu Asp Asp Ser Gly Ala Ile Ser Glu Lys Gly Ile

aac aaa ctc acc tca gca gtc ggg gaa gca gca gac cta gcg aaa acg 307 Asn Lys Leu Thr Ser Ala Val Gly Glu Ala Ala Asp Leu Ala Lys Thr 55 6Ò 65

	•	WO 0	1/0080	04										4		PCT/IB00/00922	?
	Gly					ı Met					Sei				tcc Ser 85	355	
gcc Ala	Thr	aac Asr	age Sei	gae Glu	ı Ala	a gto a Val	g cto Lev	gad Ası	cac His	: Val	g gaç L Glu	g aaq 1 Lys	g gaa Glu	a acc Thr 100	ggc Gly	403	
				c Ile					Asp					Thr	ttc Phe	451	
			Arc					Trp					Ile		aac Asn	499	
		Ile					Leu					Gly			gaa Glu	547	
											Ala				acc Thr 165	595	
					acc Thr											643	
					gat Asp											691	
					gcg Ala											739	
Arg					ctg Leu											787	
cac His 230																835	
ttt Phe	atc Ile	tca Ser	cga Arg	atg Met 250	act Thr	gcg Ala	gcg Ala	gac Asp	cgc Arg 255	gct Ala	gag Glu	ctg Leu	gaa Glu	ggt Gly 260	atc Ile	883	
agc s							Ile									931	
gct (Ala A	Ala					Asp					Glu					979	

gca ctt cgt gaa ggt gtg atc ctc acc agg atc gac aaa gga ctc gag



Ala Leu Arg Glu Gly Val Ile Leu Thr Arg Ile Asp Lys Gly Leu Glu

taacatttac ccggaaagga gtt

1050

<210> 110

<211> 309

<212> PRT

<213> Corynebacterium glutamicum

<400> 110

Val Arg Leu Gly Val Leu Asp Val Gly Ser Asn Thr Val His Leu Val 1 5 10 15

Ala Val Asp Ala Arg Pro Gly Gly His Pro Thr Pro Met Ser Asn Trp
20 25 30

Arg Thr Pro Leu Arg Leu Val Glu Leu Leu Asp Asp Ser Gly Ala Ile 35 40 45

Ser Glu Lys Gly Ile Asn Lys Leu Thr Ser Ala Val Gly Glu Ala Ala 50 55 60

Asp Leu Ala Lys Thr Leu Gly Cys Ala Glu Leu Met Pro Phe Ala Thr 65 70 75 80

Ser Ala Val Arg Ser Ala Thr Asn Ser Glu Ala Val Leu Asp His Val 85 90 95

Glu Lys Glu Thr Gly Val Arg Leu Ser Ile Leu Ser Gly Glu Asp Glu 100 105 110

Ala Arg Gln Thr Phe Leu Ala Val Arg Arg Trp Tyr Gly Trp Ser Ala 115 120 125

Gly Arg Ile Thr Asn Leu Asp Ile Gly Gly Gly Ser Leu Glu Leu Ser 130 135 140

Ser Gly Thr Asp Glu Ser Pro Asp Leu Ala Phe Ser Leu Asp Leu Gly 145 150 155 160

Ala Gly Arg Leu Thr His Asn Trp Phe Asp Thr Asp Pro Pro Ala Arg 165 170 175

Lys Lys Ile Asn Leu Leu Arg Asp Tyr Ile Asp Ala Glu Leu Ala Glu 180 185 190

Pro Ala Arg Gln Met Arg Thr Leu Gly Pro Ala Arg Leu Ala Val Gly 195 200 205

Thr Ser Lys Thr Phe Arg Thr Leu Ala Arg Leu Thr Gly Ala Ala Pro 210 215 220

Ser Ser Ala Gly Pro His Val Thr Arg Thr Leu Thr Ala Pro Gly Leu 225 230 235 240

WO 01/00804 PCT/IB00/00922

Arg Gln Leu Ile Ala Phe Ile Ser Arg Met Thr Ala Ala Asp Arg Ala Glu Leu Glu Gly Ile Ser Ser Asp Arg Ser His Gln Ile Val Ala Gly 270 260 265 Ala Leu Val Ala Glu Ala Ala Met Arg Ala Leu Asp Ile Asp Lys Val 280 Glu Ile Cys Pro Trp Ala Leu Arg Glu Gly Val Ile Leu Thr Arg Ile Asp Lys Gly Leu Glu 305 <210> 111 <211> 534 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (101)..(511) <223> RXS02972 <400> 111 acctacgacg gtgaaatcct aggctcccac tcaacccaaa tgggatgcgt gcgcctgacc 60 gaacgaatca tgcgcagcga cccacccgac tgaaaccgaa gtg gaa atc gcc cgc Val Glu Ile Ala Arg gac tac gtt gca gaa cgc atc cag gaa gta aaa gcc atc gtc cca att 163 Asp Tyr Val Ala Glu Arg Ile Gln Glu Val Lys Ala Ile Val Pro Ile tca aag gca aaa acc ttt gtg gga tgc gca ggc acc ttc acc aca atc 211 Ser Lys Ala Lys Thr Phe Val Gly Cys Ala Gly Thr Phe Thr Thr Lle tcc gcc tgg gtg caa ggc cta gaa agc tac gac cgc gac gcg atc cac 259 Ser Ala Trp Val Gln Gly Leu Glu Ser Tyr Asp Arg Asp Ala Ile His ctc tct gca ctc aac ttc gat gca ctg cga gtt gtc acc gat gag atc 307 Leu Ser Ala Leu Asn Phe Asp Ala Leu Arg Val Val Thr Asp Glu Ile att tca gaa tca tca tca cag cgc gcc agc aac cca gtt gtt gat cca 355 Ile Ser Glu Ser Ser Ser Gln Arg Ala Ser Asn Pro Val Val Asp Pro 70 80 ggt cgc gcc gac gtc atc ggt ggc gga tcc gtt gtt gtc caa gca gcg 403 Gly Arg Ala Asp Val Ile Gly Gly Gly Ser Val Val Val Gln Ala Ala

100

Ile Asp Leu Ala Ser Lys Glu Ala Gly Val Asp Tyr Ile Ile Ile Ser 105 110

gaa aaa gac atc ctc gac ggc ctc atc ctt ggc ctg gta gaa gcc gac 499 Glu Lys Asp Ile Leu Asp Gly Leu Ile Leu Gly Leu Val Glu Ala Asp 125 120

534 tct ttg aag aaa taggacccta gttttaaacc act Ser Leu Lys Lys 135

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<212> PRT <213> Corynebacterium glutamicum

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Ala Ile Val Pro Ile Ser Lys Ala Lys Thr Phe Val Gly Cys Ala Gly

Thr Phe Thr Thr Ile Ser Ala Trp Val Gln Gly Leu Glu Ser Tyr Asp

Arg Asp Ala Ile His Leu Ser Ala Leu Asn Phe Asp Ala Leu Arg Val

Val Thr Asp Glu Ile Ile Ser Glu Ser Ser Ser Gln Arg Ala Ser Asn

Pro Val Val Asp Pro Gly Arg Ala Asp Val Ile Gly Gly Gly Ser Val

Val Val Gln Ala Ala Ile Asp Leu Ala Ser Lys Glu Ala Gly Val Asp 110 100

Tyr Ile Ile Ile Ser Glu Lys Asp Ile Leu Asp Gly Leu Ile Leu Gly 125 120

Leu Val Glu Ala Asp Ser Leu Lys Lys 135

<210> 113

<211> 636

<212> DNA

<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (101)..(613)

<223> RXA02159

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act	gcto	gtg	tggc	etget	gg c	caac	cago	c ga	ggta	agac		Ser			tca Ser 5	115
					Glu					Val					cgc Arg	163
				Leu		att Ile									cag Gln	211
			Ser			ctg Leu										259
		Leu				ctc Leu 60										307
						tac Tyr										355
						ggt Gly										403
						aca Thr										451
						gcc Ala										499
Val		Leu	Lys	Glu	Val	gtt Val 140	Gly	Thr	Ile	Āla	Gly	Asp				547
ttc Phe 150	gtt Val	ctc Leu	gcc Ala	cgt Arg	gat Asp 155	ccg Pro	ctc Leu	aca Thr	ggt Gly	aaa Lys 160	gaa Glu	cta Leu	ggt Gly	gaa Glu	tta Leu 165	595
				acc Thr 170		taaa	gcgc	cc c	tagt	tcaa	g gc	t				636

<210> 114

<211> 171 <212> PRT

<213> Corynebacterium glutamicum

Met Ser Leu Gly Ser Thr Pro Ser Thr Pro Glu Asn Leu Asn Pro Val

Thr Arg Thr Ala Arg Gln Ala Leu Ile Leu Gln Ile Leu Asp Lys Gln

Lys Val Thr Ser Gln Val Gln Leu Ser Glu Leu Leu Asp Glu Gly

Ile Asp Ile Thr Gln Ala Thr Leu Ser Arg Asp Leu Asp Glu Leu Gly

Ala Arg Lys Val Arg Pro Asp Gly Gly Arg Ala Tyr Tyr Ala Val Gly

Pro Val Asp Ser Ile Ala Arg Glu Asp Leu Arg Gly Pro Ser Glu Lys

Leu Arg Arg Met Leu Asp Glu Leu Leu Val Ser Thr Asp His Ser Gly

Asn Ile Ala Met Leu Arg Thr Pro Pro Gly Ala Ala Gln Tyr Leu Ala

Ser Phe Ile Asp Arg Val Gly Leu Lys Glu Val Val Gly Thr Ile Ala

Gly Asp Asp Thr Val Phe Val Leu Ala Arg Asp Pro Leu Thr Gly Lys

Glu Leu Gly Glu Leu Leu Ser Gly Arg Thr Thr

<210> 115

<400> 114

<211> 486

<212> DNA

<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (101)..(463)

<223> RXA02201

<400> 115

totaccagoo aaatcatcaa otcatagoga aggaatcaac ttoatgaata atcaaccato 60

agtacttttc gtttgcgtcg gcaatggtgg aaaatctcaa atg gcc gca gcg cta 115 Met Ala Ala Leu 1

gcc aaa aaa cat gcc ggg gac gct ctc aaa gtt tat tca gct ggc aca 163 Ala Lys Lys His Ala Gly Asp Ala Leu Lys Val Tyr Ser Ala Gly Thr 10 20 15

aag cca ggt acg aaa tta aat caa cag tcc ctt gat tcc att gct gaa 211

	V	VO 01	/0080	4		•)									PCT/IB00/00922
Lys	Pro	Gly	Thr 25	Lys	Leu	Asn	Gln	Gln 30	Ser	Leu	Asp	Ser	Ile 35	Ala	Glu	
			gat Asp													259
		_	cga Arg	_	_	_		-				-	_			307
			cct Pro													355
-	-		tct Ser	_	_			_		_	_	-	_	_	_	403
			gat Asp 105													451
		aac Asn 120	gca Ala	tago	agtt	tt c	taat:	ctca	c ac	:a						486

<210> 116

<211> 121

<212> PRT

<213> Corynebacterium glutamicum

<400> 116

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Tyr Ser Ala Gly Thr Lys Pro Gly Thr Lys Leu Asn Gln Gln Ser Leu 20 25 30 -

Asp Ser Ile Ala Glu Val Gly Ala Asp Met Ser Gln Gly Phe Pro Lys 35 40 45

Gly Ile Asp Gln Glu Leu Ile Lys Arg Val Asp Arg Val Val Ile Leu
50 60

Gly Ala Glu Ala Gln Leu Glu Met Pro Ile Asp Ala Asn Gly Ile Leu 65 70 75 80

Gln Arg Trp Val Thr Asp Glu Pro Ser Glu Arg Gly Ile Glu Gly Met 85 90 95

Glu Arg Met Arg Leu Val Arg Asp Asp Ile Asp Ala Arg Val Gln Asn 100 105 110

Leu Val Ala Glu Leu Thr Gln Asn Ala 115 120

<211> 129 <212> PRT

<21 <21	10> 1 1> 5 12> [13> 0	510 ONA	nebad	cteri	ium g	gluta	ımiçu	ım								-
<22	21> C 22> ()(4)599	187)												
	0> 1							~ +-	****			aatt	+ = +	ataa	+a++a+	60
_		_			tt a						atg		tca	gtt		115
					aat 'Asn					Gln						163
				Ala	tca Ser											211
aag Lys	cct Pro	gca Ala 40	Gln	ggg Gly	cta Leu	aac Asn	caa Gln 45	ttg Leu	tct Ser	gtg Val	gaa Glu	tcc Ser 50	atc Ile	gct Ala	gag Glu	259
		Ala			tcg Ser											307
					gat Asp 75											355
					tct Ser											403
					caa Gln											451
					gtc Val							taaç	cgco	ega		497
aaaa	gggg	gca t	gt												÷	510
<210	> 11	18											•			

<213> Corynebacterium glutamicum

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Met Ala Ala Leu Ala Gln Lys Tyr Ala Ser Asp Ser Val Glu Ile

His Ser Ala Gly Thr Lys Pro Ala Gln Gly Leu Asn Gln Leu Ser Val

Glu Ser Ile Ala Glu Val Gly Ala Asp Met Ser Gln Gly Ile Pro Lys
50 60

Ala Ile Asp Pro Glu Leu Leu Arg Thr Val Asp Arg Val Val Ile Leu
65 70 75 80

Gly Asp Asp Ala Gln Val Asp Met Pro Glu Ser Ala Gln Gly Ala Leu 85 90 . 95

Glu Arg Trp Ser Ile Glu Glu Pro Asp Ala Gln Gly Met Glu Arg Met
100 105 110

Arg Ile Val Arg Asp Gln Ile Asp Asn Arg Val Gln Ala Leu Leu Ala 115 120 125

Gly

<210> 119

<211> 1221

<212> DNA

<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (101)..(1198)

<223> RXA00600

<400> 119

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catcgatatt gaaggtattt ttatatcggc aaacatcaat atg att gaa ggc tgg 115 Met Ile Glu Gly Trp 1 5

ctc atg acc ctt act aaa gag cat tcg aca cct cga gcg gct ggc tca 163 Leu Met Thr Leu Thr Lys Glu His Ser Thr Pro Arg Ala Ala Gly Ser 10 15 20

atg tcg ttt ctt gac cgc tgg tta gct gcc tgg att ttc ttg gct atg 211 Met Ser Phe Leu Asp Arg Trp Leu Ala Ala Trp Ile Phe Leu Ala Met 25 30 35

gct gct ggg ttg tta atc ggc aag gtc ttt cca gga att ggg gcg ctt 259

Ala	a Ala	Gly 40		ı Lev	ı Ile	Gly	, Lys 45	_	Phe	e Pro	Gly	7 Ile 50	Ala	Leu	
		Ala					, Gly					Ile		ggt	307
	Ile					Pro					. Val			aaa Lys 85	355
					Thr			gct Ala		Met					403
				Val					Met				Trp	ctg Leu	451
			Asp					Arg						ggc Gly	499
		Arg						ttg Leu							547
	Asp							ctg Leu			Ile				595
								ggt Gly							643
								acg Thr 190							691
								ttc Phe							739
								gaa Glu							787
								att							835
			Thr					ttt Phe							883
								cgt Arg							931

270 275

tac ttt gtg ggc atg ttt ttc att tcc ctg gtg gta tcc aaa ctg tcc Tyr Phe Val Gly Met Phe Phe Ile Ser Leu Val Val Ser Lys Leu Ser 285 280 ggg tta act tat gag cga gct gct tcc gtg tct ttt act gca gca gga 1027 Gly Leu Thr Tyr Glu Arg Ala Ala Ser Val Ser Phe Thr Ala Ala Gly 295 aac aac ttt gaa tta gcg att gcg gta tcg atc gga acc ttt ggt gcg 1075 Asn Asn Phe Glu Leu Ala Ile Ala Val Ser Ile Gly Thr Phe Gly Ala aca toa cog cag goa tta got gga acg atc ggc cot ttg att gaa gtc 1123 Thr Ser Pro Gln Ala Leu Ala Gly Thr Ile Gly Pro Leu Ile Glu Val 330 cca gta tta gtc gga ttg gtt tat gtc atg ttg tgg ctt gga cca aaa 1171 Pro Val Leu Val Gly Leu Val Tyr Val Met Leu Trp Leu Gly Pro Lys 345 atc ttt aaa aag gag aat gca gga tca tgaaatcagt tttgtttgtg 1218 Ile Phe Lys Lys Glu Asn Ala Gly Ser 360 1221 tgc

<210> 120 <211> 366

<212> PRT

<213> Corynebacterium glutamicum

<400> 120

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Arg Ala Ala Gly Ser Met Ser Phe Leu Asp Arg Trp Leu Ala Ala Trp

Ile Phe Leu Ala Met Ala Ala Gly Leu Leu Ile Gly Lys Val Phe Pro 40

Gly Ile Gly Ala Leu Leu Ser Ala Val Glu Ile Gly Gly Ile Ser Ile

Pro Ile Ala Ile Gly Leu Ile Val Met Met Tyr Pro Pro Leu Ala Lys

Val Arg Tyr Asp Lys Thr Lys Glu Ile Ser Thr Asp Arg Ala Leu Met

Val Val Ser Ile Met Leu Asn Trp Ile Val Gly Pro Ala Leu Met Phe

Ser Leu Ala Trp Leu Phe Leu Pro Asp Gln Pro Glu Leu Arg Thr Gly

115 120 125

Leu Ile Ile Val Gly Leu Ala Arg Cys Ile Ala Met Val Leu Val Trp 130 135 . 140

Ser Asp Leu Ala Cys Gly Asp Arg Glu Ala Thr Ala Val Leu Val Ala 145 150 155 160

Ile Asn Ser Val Phe Gln Ile Leu Met Phe Gly Val Leu Gly Trp Phe 165 170 175

Tyr Leu Gln Ile Leu Pro Ser Trp Leu Gly Leu Asp Thr Thr Ser Val 180 185 190

Thr Phe Ser Val Val Ser Ile Val Thr Ser Val Leu Val Phe Leu Gly
195 200 205

Ile Pro Leu Val Ala Gly Val Leu Ser Arg Val Ile Gly Glu Lys Thr 210 215 220

Lys Gly Arg Arg Trp Tyr Glu Asp Thr Phe Leu Pro Lys Ile Ser Pro 225 230 235 240

Leu Ala Leu Ile Gly Leu Leu Tyr Thr Ile Val Leu Leu Phe Ser Leu 245 250 255

Gln Gly Asp Glu Ile Thr Ala Gln Pro Trp Thr Val Ala Arg Leu Ala 260 265 270

Leu Pro Leu Leu Met Tyr Phe Val Gly Met Phe Phe Ile Ser Leu Val 275 280 285

Val Ser Lys Leu Ser Gly Leu Thr Tyr Glu Arg Ala Ala Ser Val Ser 290 295 300

Phe Thr Ala Ala Gly Asn Asn Phe Glu Leu Ala Ile Ala Val Ser Ile 305 310 315 320

Gly Thr Phe Gly Ala Thr Ser Pro Gln Ala Leu Ala Gly Thr Ile Gly 325 330 335

Pro Leu Ile Glu Val Pro Val Leu Val Gly Leu Val Tyr Val Met Leu 340 345 350

Trp Leu Gly Pro Lys Ile Phe Lys Lys Glu Asn Ala Gly Ser 355 360 365

<210> 121

<211> 1233

<212> DNA

<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (101)..(1210)

<223> RXA02200

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					Pro					Phe	ctt Leu				Ile	163
				: Ile					Phe		cta Leu					211
			Gly					Leu			atg Met		Val			259
							Gly				atg Met 65	Met				307
Leu 70	Ala	Lys	Val	Arg	Tyr 75	Asp	Lys	Thr	Lys	Gln 80	att Ile	Ala	Thr	Asp	Lys 85	355
His	Leu	Met	Gly	Val 90	Ser	Leu	Ile	Leu	Asn 95	Trp	gtg Val	Val	Gly	Pro 100	Ala	403
Leu	Met	Phe	Ala 105	Leu	Ala	Trp	Leu	Phe 110	Leu	Pro	gac Asp	Gln	Pro 115	Glu	Leu	451
Arg	Thr	Gly 120	Leu	Ile	Ile	Val	Gly 125	Leu	Ala	Arg	tgt Cys	Ile 130	Ala	Met	Val	499
Leu	Val 135	Trp	Ser	Asp	Met	Ser 140	Cys	Gly	Asp	Arg	gag Glu 145	Ala	Thr	Ala	Val	547
Leu 150	Val	Ala	Ile	Asn	Ser 155	Val	Phe	Gln	Val	Ala 160	atg Met	Phe	Gly	Ala	Leu 165	595
ĞÎy	Trp	Phe	Tyr	Leu 170	Gln	Val	Leu	Pro	Ser 175	Trp	cta Leu	Gly	Leu	Pro 180	Thr	643
											act Thr				<i>j</i> - 3	691
ttc	ctc	gga	ata	cct	cta	ctt	gct	gga	gtt	ttc	tcg	cga	att	att	ggc	739

	V	VO 02	1/0080)4			}						٠			PCT/IB00/00922
Phe	Leú	Gly 200		Pro	Leu	Leu	Ala 205	-	Val	Phe	Ser	Arg 210		Ile	Gly	
		Ile		gga Gly			Trp					Phe				787 .
				gca Ala							Thr					835
				ggt Gly 250												883
-		-		cca Pro	_	-				-		_				931
				tca Ser					_			_	_		-	979
	_			act Thr	_	_					_					1027
				acg Thr												1075
_				ttg Leu 330		-			-		-		-	-		1123
				cta Leu			Lys									1171
	Ser		_	cgt Arg		Thr	_						tago	gaag	ga	1220
atca	actt	ca t	ga													1233

<210> 122

<211> 370

<212> PRT

<213> Corynebacterium glutamicum

<400> 122

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Leu Asp Lys Tyr Ile Pro Leu Trp Ile Ile Leu Ala Met Ala Phe Gly 20

Leu Phe Leu Gly Arg Ser Val Ser Gly Leu Ser Gly Phe Leu Gly Ala 35 40 45

Met Glu Val Gly Gly Ile Ser Leu Pro Ile Ala Leu Gly Leu Leu Val 50 55 60

Met Met Tyr Pro Pro Leu Ala Lys Val Arg Tyr Asp Lys Thr Lys Gln 65 70 75 80

Ile Ala Thr Asp Lys His Leu Met Gly Val Ser Leu Ile Leu Asn Trp 85 90 95

Val Val Gly Pro Ala Leu Met Phe Ala Leu Ala Trp Leu Phe Leu Pro 100 105 110

Asp Gln Pro Glu Leu Arg Thr Gly Leu Ile Ile Val Gly Leu Ala Arg 115 120 125

Cys Ile Ala Met Val Leu Val Trp Ser Asp Met Ser Cys Gly Asp Arg 130 135 140

Glu Ala Thr Ala Val Leu Val Ala Ile Asn Ser Val Phe Gln Val Ala 145 150 155 160

Met Phe Gly Ala Leu Gly Trp Phe Tyr Leu Gln Val Leu Pro Ser Trp 165 170 175

Leu Gly Leu Pro Thr Thr Ala Gln Phe Ser Phe Trp Ser Ile Val 180 185 190

Thr Ser Val Leu Val Phe Leu Gly Ile Pro Leu Leu Ala Gly Val Phe 195 200 205

Ser Arg Ile Ile Gly Glu Lys Ile Lys Gly Arg Glu Trp Tyr Glu Gln 210 215 220

Lys Phe Leu Pro Ala Ile Ser Pro Phe Ala Leu Ile Gly Leu Leu Tyr 225 230 235 240

Thr Ile Val Leu Leu Phe Ser Leu Gln Gly Asp Gln Ile Val Ser Gln 245 250 255

Pro Trp Ala Val Val Arg Leu Ala Ile Pro Leu Val Ile Tyr Phe Val 260 265 270

Gly Met Phe Phe Ile Ser Leu Ile Ala Ser Lys Leu Ser Gly Met Asn 275 280 285

Tyr Ala Lys Ser Ala Ser Val Ser Phe Thr Ala Ala Gly Asn Asn Phe 290 295 300

Glu Leu Ala Ile Ala Val Ser Ile Gly Thr Phe Gly Ala Thr Ser Ala 305 310 315 320

Gln Ala Met Ala Gly Thr Ile Gly Pro Leu Ile Glu Ile Pro Val Leu 325 330 335 Val Gly Leu Val Tyr Ala Met Leu Trp Leu Gly Pro Lys Leu Phe Pro 340 345 350

Asn Asp Pro Thr Leu Pro Ser Ser Ala Arg Ser Thr Ser Gln Ile Ile 355 360 365

Asn Ser 370

<210> 123

<211> 762

<212> DNA

<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (101)..(739)

<223> RXA02202

<400> 123

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aatctattgg tttccccgta aaatcttcga aaggaagaac atg acc ggg caa gct 115 Met Thr Gly Gln Ala 1 5

gca cca aac ttg cat acc aat att ttg aac cgt atc gca aat gaa ctg 163 Ala Pro Asn Leu His Thr Asn Ile Leu Asn Arg Ile Ala Asn Glu Leu 10 15 20

gcg ttg acc tat caa gga gtt ttc tct gca gag act atc aac cgc tat 211
Ala Leu Thr Tyr Gln Gly Val Phe Ser Ala Glu Thr Ile Asn Arg Tyr
25 30 35

att ttt gaa tcg tat gtg tcg ttg gcg aga aca gca aaa atc cat acg 259
Ile Phe Glu Ser Tyr Val Ser Leu Ala Arg Thr Ala Lys Ile His Thr
40 50

cac ctg cca att ttg gca gaa ggt ttt gct aaa gac cgg ctg cac gca 307 His Leu Pro Ile Leu Ala Glu Gly Phe Ala Lys Asp Arg Leu His Ala

ctt gcg gta gct gaa ggt aag gtg gct tca cct gtg cct cag gtc cta 355 Leu Ala Val Ala Glu Gly Lys Val Ala Ser Pro Val Pro Gln Val Leu 70 75 80 85

ttt att tgc gtc cac aac gca ggt cgt tca caa att gct tcg gcg ttg
Phe Ile Cys Val His Asn Ala Gly Arg Ser Gln Ile Ala Ser Ala Leu
90 95 100

ttg tct cac tat gcc ggt agt tct gta gag gta cgt tct gca ggt tct
Leu Ser His Tyr Ala Gly Ser Ser Val Glu Val Arg Ser Ala Gly Ser
105 110 115

tta cct qct tct gaa att cac cca ctg gtg ttg gaa att ttg tca gag 499

	V	VO 01.	/0080-	1		•										PCT/IB00/00922
Leu	Pro	Ala 120	Ser	Glu	Ile	His	Pro 125	Leu	Val	Leu	Glu	Ile 130	Leu	Ser	Glu	
-		gtg Val				_	-		-		-				-	
		cgc Arg														595
tgc Cys		atg Met														643

-		-		_				_		_	caa Gln	739
tago	cagt	ca a	aggt	ctg	jc ad	cc						762

ccg tca gat gaa ggt gag gac aag ata cag gaa ata att gag gaa att

Pro Ser Asp Glu Gly Glu Asp Lys Ile Gln Glu Ile Ile Glu Glu Ile 190

175

<210> 124

<211> 213

<212> PRT

<213> Corynebacterium glutamicum

. 170

<400> 124

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Thr Ile Asn Arg Tyr Ile Phe Glu Ser Tyr Val Ser Leu Ala Arg Thr

Ala Lys Ile His Thr His Leu Pro Ile Leu Ala Glu Gly Phe Ala Lys

Asp Arg Leu His Ala Leu Ala Val Ala Glu Gly Lys Val Ala Ser Pro

Val Pro Gln Val Leu Phe Ile Cys Val His Asn Ala Gly Arg Ser Gln

Ile Ala Ser Ala Leu Leu Ser His Tyr Ala Gly Ser Ser Val Glu Val

Arg Ser Ala Gly Ser Leu Pro Ala Ser Glu Ile His Pro Leu Val Leu

Glu Ile Leu Ser Glu Arg Gly Val Asn Ile Ser Asp Ala Phe Pro Lys

130 135 140

Pro Leu Thr Asp Asp Val Ile Arg Ala Ser Asp Tyr Val Ile Thr Met 145 150 155 160

Gly Cys Gly Asp Val Cys Pro Met Tyr Pro Gly Lys His Tyr Leu Asp 165 170 175

Trp Glu Leu Ala Asp Pro Ser Asp Glu Gly Glu Asp Lys Ile Gln Glu
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Ile Ile Glu Glu Ile Asp Gly Arg Ile Arg Glu Leu Trp Lys Ser Ile 195 200 205

Gln Leu Ser Gln Asn 210

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<222> (101)..(979)

<223> RXA02205

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acc ctc cta gcc gca gca gca gat cct gcc gca act gaa aat att ggc 163
Thr Leu Leu Ala Ala Ala Ala Asp Pro Ala Ala Thr Glu Asn Ile Gly

tgg gta caa acc att gtg ctc tcc atc gtt caa ggc ctc aca gag ttc 211
Trp Val Gln Thr Ile Val Leu Ser Ile Val Gln Gly Leu Thr Glu Phe
25 30 35

ctg ccg atc agc tcc agc gga cac ctc cga atc atc tct gag ctg ttc 259 Leu Pro Ile Ser Ser Ser Gly His Leu Arg Ile Ile Ser Glu Leu Phe 40 45 50

tgg ggt gcc gat gcc ggc gcg tcc ttt acc gcc gtg gtt cag ctt ggt 307 Trp Gly Ala Asp Ala Gly Ala Ser Phe Thr Ala Val Val Gln Leu Gly

acc gaa gcc gca gtg ctg gtg ttt ttt gcc aag gaa atc tgg caa atc
Thr Glu Ala Ala Val Leu Val Phe Phe Ala Lys Glu Ile Trp Gln Ile
70 75 80 85

atc aca ggt tgg ttc gct ggc gta ttc aat aag gaa cgc cgc gga ttt 403 Ile Thr Gly Trp Phe Ala Gly Val Phe Asn Lys Glu Arg Arg Gly Phe

95

100

				: Gl					₹ Va			att Ile		Val	gtg Val	451
			v Val					Lei				g gcg Ala 130	Leu		aat Asn	499
		Ile					Let					ctg Leu				547
ttg Leu 150	gcc	gag Glu	aag Lys	atg Met	ggc Gly 155	Lys	aag Lys	gaa Glu	cgc Arg	gac Asp 160	Tyr	gac Asp	aaa Lys	ctg Leu	acc Thr 165	595
										Gln		ctt Leu				643
												ggt Gly				691
ggt Gly	ctc Leu	aag Lys 200	cgt Arg	gaa Glu	gta Val	gcc Ala	acc Thr 205	aag Lys	ttc Phe	tcc Ser	ttc Phe	ctg Leu 210	ctg Leu	gca Ala	atc Ile	739
												gac Asp				787
cca Pro 230	agc Ser	tcc Ser	gga Gly	caa Gln	gct Ala 235	gcc Ala	tcc Ser	ggc Gly	cta Leu	cag Gln 240	ctc Leu	acc Thr	gtg Val	ggt Gly	acc Thr 245	835
ctg Leu	gtt Val	gcc Ala	Phe	gta Val 250	gtt Val	ggc Gly	tac Tyr	att Ile	tcc Ser 255	att Ile	gcg Ala	tgg. Trp	ctg Leu	atg Met 260	aag Lys	883
ttc Phe	gtg Val	Ala	aac Asn 265	cac His	tcc Ser	ttc Phe	agc Ser	tgg Trp 270	ttt Phe	gct Ala	gca Ala	Tyr	cgt Arg 275	att Ile	cct Pro	931
gca Ala	Gly	ctg Leu 280	ctc Leu	gtg Val	atg Met	Leu	ctg Leu 285	ctc Leu	gca Ala	ctg Leu	ggc Gly	atg Met 290	ctc Leu	aac Asn	cca Pro	979
taaa	attc	ct g	taca	tctt	a aa	a										1002

<210> 126

<211> 293

<212> PRT

<213> Corynebacterium glutamicum

Thr Glu Asn Ile Gly Trp Val Gln Thr Ile Val Leu Ser Ile Val Gln 20 25 30

Gly Leu Thr Glu Phe Leu Pro Ile Ser Ser Ser Gly His Leu Arg Ile 35 40 45

Ile Ser Glu Leu Phe Trp Gly Ala Asp Ala Gly Ala Ser Phe Thr Ala 50 55 60

Val Val Gln Leu Gly Thr Glu Ala Ala Val Leu Val Phe Phe Ala Lys
65 70 75 80

Glu Ile Trp Gln Ile Ile Thr Gly Trp Phe Ala Gly Val Phe Asn Lys 85 90 95

Glu Arg Arg Gly Phe Glu Tyr Arg Met Gly Trp Met Ile Ile Val Ala 100 105 110

Thr Ile Pro Val Val Ile Leu Gly Val Leu Gly Lys Asp Leu Ile Arg 115 120 125

Glu Ala Leu Arg Asn Met Trp Ile Thr Ala Ser Val Leu Ile Leu Phe 130 135 140

Ser Leu Val Phe Ile Leu Ala Glu Lys Met Gly Lys Lys Glu Arg Asp 145 150 155 160

Tyr Asp Lys Leu Thr Met Lys Asp Ala Ile Ile Met Gly Leu Ala Gln 165 170 175

Cys Leu Ala Leu Ile Pro Gly Val Ser Arg Ser Gly Gly Thr Ile Ser 180 185 190

Ala Gly Leu Phe Leu Gly Leu Lys Arg Glu Val Ala Thr Lys Phe Ser 195 200 205

Phe Leu Leu Ala Ile Pro Ala Val Leu Gly Ser Gly Leu Tyr Ser Leu 210 215 220

Pro Asp Ala Phe Ala Pro Ser Ser Gly Gln Ala Ala Ser Gly Leu Gln 225 230 235 240

Leu Thr Val Gly Thr Leu Val Ala Phe Val Val Gly Tyr Ile Ser Ile 245 250 255

Ala Trp Leu Met Lys Phe Val Ala Asn His Ser Phe Ser Trp Phe Ala 260 265 270

Ala Tyr Arg Ile Pro Ala Gly Leu Leu Val Met Leu Leu Leu Ala Leu 275 280 285

Gly Met Leu Asn Pro

<2 <2	210> 211> 212> 213>	975 DNA	yneba	actei	rium	glut	amic	:um	•							
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											c gte Va.	g cg	t gg	t at	t gcg e Ala 5	115
cg Ar	g Ala	g at a Il	c gt e Va	g cca 1 Pro 10	o Ası	c ct	t gaa u Glu	a cgo	g Gl	y Gl	a aaq n Lys	g gct s Ala	geo Ala	g cad His	gcc Ala	163
tti Phe	gca Ala	a cto	g cte u Lei 2!	u Met	g att	att	caç e Glr	30 3 Gl 3 Gl	/ Ile	t gci e Ala	cco Pro	gto Val	g gta Val	. Ala	ccg Pro	211
cto Lev	att Ile	ggt Gly 40	/ Gly	gto Val	g cto Leu	gto Val	ggg Gly 45	Pro	tti Phe	ggc Gly	tgg Trp	g cgg Arg 50	Gly	att Ile	ttc Phe	259
tgg Trp	gca Ala 55	Let	gca Ala	ctg Leu	gtg Val	aat Asn 60	Phe	gcg Ala	Glr	ctg Leu	ctt Leu 65	Val	gct Ala	ttg Leu	ctg Leu	307
cag Gln 70	Ile	aag Lys	gag Glu	tcg Ser	aag Lys 75	cca Pro	gtt Val	gaa Glu	gag Glu	cgt Arg 80	Thr	gca Ala	gca Ala	gga Gly	ctt Leu _85	355
ggc	gga Gly	atg Met	ctg Leu	tcc Ser 90	aac Asn	tat Tyr	gtc Val	ttt Phe	gtg Val 95	ctg Leu	aag Lys	aat Asn	cct Pro	caa Gln 100	ttt Phe	403
ttg Leu	gca Ala	tat Tyr	gta Val 105	ttc Phe	aca Thr	ttg Leu	Gly ggg	ctg Leu 110	tct Ser	ttt Phe	ggg Gly	gcg Ala	atg Met 115	ttc Phe	tcc Ser	451
tac Tyr	att Ile	tcg Ser 120	gcg Ala	tcg Ser	ccg Pro	ttc Phe	gtg Val 125	ctg Leu	cag Gln	aat Asn	caa Gln	atg Met 130	ggc Gly	att Ile	ccg Pro	499
gta Val	ctg Leu 135	ctg Leu	tat Tyr	tcc Ser	att Ile	att Ile 140	ttc Phe	gga Gly	gtg Val	aat Asn	gct Ala 145	ttt Phe	ggt Gly	ttg Leu	att Ile	547
gtg	ggc	gga	atg	gtc	aat	agg	cga	ctt	ctg	cag	cgg	att	cat	cca	cac	595

-	V	VO 01	/0080	4		•	-									PCT/IB00/00922
Val 150	-	Gly	Met	: Val	Asn 155		Arg	Leu	Leu	Gln 160		Ile	His	Pro	His 165	
cgc Arg	ato	atg Met	caa Gln	act Thr 170	Val	ctg Leu	gcc Ala	agt Ser	ttt Phe 175	Thr	gtg Val	ctg Leu	tgt Cys	gcg Ala 180	ctt Leu	643
			gaa Glu 185	Val					Trp							691
			ctt Leu													739
			gga Gly													787
			ggt Gly													835
			tta Leu													883
		Cys	gca Ala	Leu		Ala	Cys	Gly	Cys	Ala	Tyr		Ala	Gly		931

<210> 128 <211> 284 <212> PRT <213> Corynebacterium glutamicum

Lys Gly Ile Pro Glu Met Lys

280

270

aaa ggt att cca gaa atg aag tagctctagg tggcgtttta agg

975

Lys Ala Ala His Ala Phe Ala Leu Leu Met Ile Ile Gln Gly Ile Ala 20 25 30

Pro Val Val Ala Pro Leu Ile Gly Gly Val Leu Val Gly Pro Phe Gly 35 40 45

Trp Arg Gly Ile Phe Trp Ala Leu Ala Leu Val Asn Phe Ala Gln Leu 50 55 60

Leu Val Ala Leu Leu Gln Ile Lys Glu Ser Lys Pro Val Glu Glu Arg
65 70 · 75 80

WO 01/00804 Thr Ala Ala Gly Leu Gly Gly Met Leu Ser Asn Tyr Val Phe Val Leu Lys Asn Pro Gln Phe Leu Ala Tyr Val Phe Thr Leu Gly Leu Ser Phe 100 105 110 Gly Ala Met Phe Ser Tyr Ile Ser Ala Ser Pro Phe Val Leu Gln Asn Gln Met Gly Ile Pro Val Leu Leu Tyr Ser Ile Ile Phe Gly Val Asn 130 Ala Phe Gly Leu Ile Val Gly Gly Met Val Asn Arg Arg Leu Leu Gln Arg Ile His Pro His Arg Ile Met Gln Thr Val Leu Ala Ser Phe Thr 165 Val Leu Cys Ala Leu Leu Leu Ile Glu Val Leu Phe Ile Asn Trp Ile Pro Leu Phe Leu Leu Leu Phe Leu Ile Val Ser His Ile Pro Met 195 Val Met Ala Asn Ala Thr Ala Leu Gly Thr Glu Val Val Arg Ser Arg Ala Gly Ser Gly Ser Ala Ile Leu Gly Phe Val Gln Phe Thr Met Gly 225 Ala Leu Val Ser Ser Leu Val Gly Leu Gly Ser Asp Lys Ala Leu Thr Met Gly Ile Ala Met Thr Ala Cys Ala Leu Leu Ala Cys Gly Cys Ala Tyr Leu Ala Gly Arg Lys Gly Ile Pro Glu Met Lys 275

<210> 129 <211> 537 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (101)..(514)

<223> RXN00901 <400> 129

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aaataccccc aaatcttcga tatagataca cgagacagtg atg cag aaa aaa caa 115 Met Gln Lys Lys Gln 1 5

WO 01/0080	4			PCT/IB00/00922
cag ctg agc acc Gln Leu Ser Thi	c gcc ctg att a c Ala Leu Ile M 10	atg gga ttg go Met Gly Leu Al 15	ca tta ttg tca gcc ag la Leu Leu Ser Ala Se 20	c 163 r
tcc gcg cta gcg Ser Ala Leu Ala 25	Thr Asp Met T	at ttg ccg go Tyr Leu Pro Al	ca atg cct ggt att gc la Met Pro Gly Ile Al 35	g 211 a
gaa gat ttg ggg Glu Asp Leu Gly 40	Thr Thr Ala P	ccg atg gtg ca Pro Met Val GI 45	ag tta act ctt tct tc In Leu Thr Leu Ser Se 50	c 259 r
ttt atg gct gga Phe Met Ala Gly 55	atg gcg att g Met Ala Ile G 60	gc caa ttg at ly Gln Leu Il	cc att ggt cct ttg tc le Ile Gly Pro Leu Se 65	g 307 r
		eu Leu Val Al	ca ggt gcg gtg gct gc .a Gly Ala Val Ala Al 0 8	a.
			ng tog ata ago gta tt no Ser Ile Ser Val Le 100	
gtg atc gca cgc Val Ile Ala Arg 105	ctg gtg cag go Leu Val Gln G	gg ctt ggc gg ly Leu Gly Gl 110	c ggt gcg tgc gtg gt y Gly Ala Cys Val Va 115	a 451 1
	Ser Cys Gln Th		g gac aaa agg ctg cg a Asp Lys Arg Leu Ard 130	
acg cct ttg cac Thr Pro Leu His 135	-	t tcagggaatt	gct	537
<210> 130 <211> 138 <212> PRT <213> Corynebact	erium glutamic	cum	-	
<400> 130 Met Gln Lvs Lvs	Gln Gln Leu Se	or Thr Ala Lei	ı Ile Met Gly Leu Ala	
1	5	10	15	
Leu Leu Ser Ala 20	Ser Ser Ala Le	u Ala Thr Asp 25	Met Tyr Leu Pro Ala 30	ı
Met Pro Gly Ile 35	Ala Glu Asp Le 4	_	Ala Pro Met Val Glm 45	i.
Leu Thr Leu Ser	Ser Phe Met Ala	a Gly Met Ala	Ile Gly Gln Leu Ile	

Ile Gly Pro Leu Ser Asp Gln Leu Gly Arg Lys Gly Leu Leu Val Ala 65 70 75 80

Gly Ala Val Ala Ala Leu Val Ala Ser Val Val Cys Ala Leu Ala Pro Ser Ile Ser Val Leu Val Ile Ala Arg Leu Val Gln Gly Leu Gly Gly Gly Ala Cys Val Val Leu Arg Ala Arg Ser Cys Gln Thr Leu Asn Ala 115 120 Asp Lys Arg Leu Arg Thr Pro Leu His Cys 130 135 <210> 131 <211> 501 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (101)..(478) <223> FRXA00901 <400> 131 acctgaatga aaatttctaa ttaaaaatac ccccaaatct tcgatataga tacacqagac 60 agtgatgcag aaaaaacaac agctgagcac cgccctgatt atg gga ttg gca tta 115 Met Gly Leu Ala Leu ttg tca gcc agc tcc gcg cta gcg act gat atg tat ttg ccg gca atg 163 Leu Ser Ala Ser Ser Ala Leu Ala Thr Asp Met Tyr Leu Pro Ala Met cct ggt att gcg gaa gat ttg ggg aca act gca ccg atg gtg cag tta 211 Pro Gly Ile Ala Glu Asp Leu Gly Thr Thr Ala Pro Met Val Gln Leu 30 act ctt tct tcc ttt atg gct gga atg gcg att ggc caa ttg atc att 259 Thr Leu Ser Ser Phe Met Ala Gly Met Ala Ile Gly Gln Leu Ile Ile ggt cct ttg tcg gat caa ttg gga agg aaa ggc ctg ctc gtt gca ggt 307 Gly Pro Leu Ser Asp Gln Leu Gly Arg Lys Gly Leu Leu Val Ala Gly gcg gtg gct gcg ctg gtc gct agt gtg gtg tgc gcg ctg gcg ccg tcg 355 Ala Val Ala Ala Leu Val Ala Ser Val Val Cys Ala Leu Ala Pro Ser ata ago gta tta gtg ato gca cgc ctg gtg cag ggg ctt ggc ggt 403 Ile Ser Val Leu Val Ile Ala Arg Leu Val Gln Gly Leu Gly Gly Gly

gcg tgc gtg gta ttg cgc gcg cga tcg tgc cag acc ttg aac gcg gac

Ala Cys Val Val Leu Arg Ala Arg Ser Cys Gln Thr Leu Asn Ala Asp

110

115

aaa agg ctg cgc acg cct ttg cac tgc tgatgattat tcagggaatt 498
Lys Arg Leu Arg Thr Pro Leu His Cys
120 125

gct 501

<210> 132

<211> 126

<212> PRT

<213> Corynebacterium glutamicum

<400> 132

Met Gly Leu Ala Leu Leu Ser Ala Ser Ser Ala Leu Ala Thr Asp Met

1 5 10 15

Tyr Leu Pro Ala Met Pro Gly Ile Ala Glu Asp Leu Gly Thr Thr Ala 20 25 30

Pro Met Val Gln Leu Thr Leu Ser Ser Phe Met Ala Gly Met Ala Ile 35 40 45

Gly Gln Leu Ile Ile Gly Pro Leu Ser Asp Gln Leu Gly Arg Lys Gly
50 55 60

Leu Leu Val Ala Gly Ala Val Ala Ala Leu Val Ala Ser Val Val Cys
65 70 75 80

Ala Leu Ala Pro Ser Ile Ser Val Leu Val Ile Ala Arg Leu Val Gln
85 90 95

Gly Leu Gly Gly Ala Cys Val Val Leu Arg Ala Arg Ser Cys Gln 100 105 110

Thr Leu Asn Ala Asp Lys Arg Leu Arg Thr Pro Leu His Cys 115 120 125

<210> 133

<211> 1299

<212> DNA

<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (101)..(1276)

<223> RXA00289

<400> 133

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accccattaa acagcccgat tcaagaaagg cttcgcagcc atg agc acc acc acc 115

Met Ser Thr Thr Thr

1 5

gcg Ala	ccc	gaa Glu	gca Ala	cgg Arg 10	ttt Phe	cct	gtc Val	gtc Val	cct Pro 15	ttg Leu	acc Thr	gcc Ala	atg Met	agt Ser 20	ttc Phe	163
gcg Ala	gca Ala	ttt Phe	gtt Val 25	tat Tyr	gtc Val	acg Thr	ttc Phe	gag Glu 30	atg Met	ttt Phe	gca Ala	gtt Val	ggc Gly 35	ctc Leu	atc Ile	211
aag Lys	ccg Pro	atg Met 40	gcc Ala	agc Ser	gat Asp	ctt Leu	gga Gly 45	gtg Val	tca Ser	gaa Glu	tcc Ser	agc Ser 50	atc Ile	ggc Gly	ctg Leu	259
ttg Leu	atg Met 55	act Thr	gtg Val	tat Tyr	gcg Ala	act Thr 60	gtc Val	gtt Val	gcc Ala	gtg Val	gtg Val 65	acg Thr	atc Ile	cct Pro	gcc Ala	307
atg Met 70	ttg Leu	tgg Trp	gtt Val	tct Ser	cga Arg 75	ttt Phe	aac Asn	aag Lys	cgc Arg	aca Thr 80	gtt Val	ttc Phe	ctg Leu	att Ile	act Thr 85	355
ctg Leu	gca Ala	ttt Phe	ttg Leu	gcc Ala 90	acg Thr	ggc Gly	att Ile	gtt Val	gtt Val 95	cag Gln	gca Ala	ctg Leu	acc Thr	gtt Val 100	aat Asn	403
tat Tyr	gga Gly	atg Met	cta Leu 105	gcc Ala	atc Ile	ggc Gly	cgc Arg	act Thr 110	atc Ile	gca Ala	gca Ala	ttg Leu	act Thr 115	cac His	ĠĮÀ Ġđđ	451
gtg Val	ttt Phe	tgg Trp 120	gca Ala	ctt Leu	gtt Val	GJ Å GG Å	cca Pro 125	atg Met	gca Ala	gcg Ala	cgt Arg	atg Met 130	tcc Ser	cca Pro	ggt Gly	499
cac	act Thr 135	ggt Gly	cgt Arg	gca Ala	gta Val	ggc Gly 140	gtt Val	gtg Val	tcg Ser	att Ile	gga Gly 145	tca Ser	acc Thr	atg Met	gcg Ala	547
ctg Leu 150	gtc Val	gtt Val	ggt Gly	tct Ser	ccg Pro 155	ctg Leu	gca Ala	aca Thr	tgg Trp	atc Ile 160	ggt Gly	gaa Glu	ctc Leu	atc Ile	gga Gly 165	595
tgg Trp	cgt Arg	cct Pro	gcc Ala	acc Thr 170	tgg Trp	att Ile	ctt Leu	ggt Gly	gcg Ala 175	ctg Leu	acc Thr	att Ile	gcg Ala	gcc Ala 180	gtg Val	643
gct Ala	gta Val	ctc Leu	att Ile 185	cca Pro	acc Thr	gtt Val	cca Pro	tca Ser 190	ctg Leu	cca Pro	cca Pro	ctt Leu	cca Pro 195	gac Asp	acg Thr	691
gaa Glu	tca Ser	gag Glu 200	tcc Ser	aaa Lys	gaa Glu	aag Lys	aaa Lys 205	tcc Ser	ctt Leu	cca Pro	tgg Trp	ggt Gly 210	ctc Leu	att Ile	tcc Ser	739
ctg Leu	gtc Val 215	att Ile	ttc Phe	ctt Leu	ctc Leu	ctt Leu 220	gcc Ala	gtc Val	acc Thr	ggt Gly	gtt Val 225	ttt Phe	gct Ala	gcc Ala	tac Tyr	787
acc	tac	ctt	ggc	ctc	atc	atc	gct	gaa	aca	gca	ggg	gac	agc	ttc	gtg	835

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Thr 230	-	Leu	Gly	Leu	Ile 235		Ala	Glu	Thr	Ala 240	_	Asp	Ser	Phe	Val 245	
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gtg Val	gca Ala	acc Thr	cga Arg 265	act Thr	gtg Val	gat Asp	caa Gln	cgc Arg 270	atg Met	ctg Leu	cgt Arg	gga Gly	agt Ser 275	gtt Val	cac His	931
acc Thr	acc Thr	act Thr 280	ttg Leu	ttt Phe	gtc Val	att Ile	gct Ala 285	gca Ala	att Ile	ctc Leu	gga Gly	cag Gln 290	atc Ile	gca Ala	ttc Phe	979
									gct Ala							1027
									cca Pro							1075
									gat Asp 335							1123
		Thr							tct Ser							1171
									ggc Gly							1219
					Ser				ttg Leu							1267
cta Leu 390	_	-	tagc	agcc	ca a	attc	agcc	c ac	t						-	1299
<210 <211 <212 <213	> 39 > PR	2 T	bacto	eriu	m gl	utam.	icum									
<400 Met 1			Thr '	Thr i	Ala :	Pro (Glu /	Ala i	Arg	Phe	Pro '	Val	Val	Pro 15	Leu	

Thr Ala Met Ser Phe Ala Ala Phe Val Tyr Val Thr Phe Glu Met Phe 20 25 30

Ala Val Gly Leu Ile Lys Pro Met Ala Ser Asp Leu Gly Val Ser Glu

WO 01/00804 40 35 45 Ser Ser Ile Gly Leu Leu Met Thr Val Tyr Ala Thr Val Val Ala Val Val Thr Ile Pro Ala Met Leu Trp Val Ser Arg Phe Asn Lys Arg Thr Val Phe Leu Ile Thr Leu Ala Phe Leu Ala Thr Gly Ile Val Val Gln Ala Leu Thr Val Asn Tyr Gly Met Leu Ala Ile Gly Arg Thr Ile Ala Ala Leu Thr His Gly Val Phe Trp Ala Leu Val Gly Pro Met Ala Ala Arg Met Ser Pro Gly His Thr Gly Arg Ala Val Gly Val Val Ser Ile Gly Ser Thr Met Ala Leu Val Val Gly Ser Pro Leu Ala Thr Trp Ile Gly Glu Leu Ile Gly Trp Arg Pro Ala Thr Trp Ile Leu Gly Ala Leu Thr Ile Ala Ala Val Ala Val Leu Ile Pro Thr Val Pro Ser Leu Pro

Pro Leu Pro Asp Thr Glu Ser Glu Ser Lys Glu Lys Lys Ser Leu Pro

Trp Gly Leu Ile Ser Leu Val Ile Phe Leu Leu Leu Ala Val Thr Gly

Val Phe Ala Ala Tyr Thr Tyr Leu Gly Leu Ile Ile Ala Glu Thr Ala

Gly Asp Ser Phe Val Ser Ile Gly Leu Phe Ala Phe Gly Ala Leu Gly

Leu Ile Gly Val Thr Val Ala Thr Arg Thr Val Asp Gln Arg Met Leu

Arg Gly Ser Val His Thr Thr Leu Phe Val Ile Ala Ala Ile Leu 280

Gly Gln Ile Ala Phe Gly Leu Glu Gly Thr Leu Ala Val Val Ala Ile

Phe Leu Ala Val Thr Val Phe Gly Gly Ala Tyr Gly Ala Leu Pro Thr

Leu Gly Thr Thr Ile Phe Leu His Ala Gly Arg Asp His Pro Asp Thr

Ala Ser Ser Ile Tyr Val Val Thr Tyr Gln Val Gly Ile Ala Ser Gly

345

350

Ala Ala Leu Gly Ala Met Ala Val Asp Ala Asp Trp Val Ala Gly Thr 355 360 365

Leu Trp Ile Met Ala Gly Leu Ser Leu Ala Ser Thr Leu Ala Leu Ala

370 375 38

Leu Trp Ser Arg Pro Leu Leu Lys 385 390

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<211> 420

<212> DNA

<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (101)..(397)

<223> RXN01984

<400> 135

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caatagtgcc ggtgagggag ctgtccgata ttgtgcttac atg cac gaa tct gga 115 Met His Glu Ser Gly 1 5

aaa aat cct gtc aag gtt gtc gac tcg cag gca cca caa gga cgc ggt 163 Lys Asn Pro Val Lys Val Val Asp Ser Gln Ala Pro Gln Gly Arg Gly 10 15 20

ggg cat atc ggc gga cat atc aaa cgc cgc ccg att cct agg caa acg 211 Gly His Ile Gly Gly His Ile Lys Arg Arg Pro Ile Pro Arg Gln Thr

gaa att tcc gag gtt cgt cga tat atc gtc atg act gcc ctc gca ctc 259 Glu Ile Ser Glu Val Arg Arg Tyr Ile Val Met Thr Ala Leu Ala Leu 40 45 50

ggt ggc ttc gcc atc ggt gtg acg gaa ttt gtc tcc atg ggt ctg ctc 307 Gly Gly Phe Ala Ile Gly Val Thr Glu Phe Val Ser Met Gly Leu Leu

age geg ate gee tee gae ttt gag ate tee gaa gae caa gee gga cae 355 Ser Ala Ile Ala Ser Asp Phe Glu Ile Ser Glu Asp Gln Ala Gly His 70 75 80 85

atc atc acc atc tac gcc ctc gcg tgg ttg tgg gtg ccc cgc 397
Ile Ile Thr Ile Tyr Ala Leu Ala Trp Leu Trp Val Pro Arg
90 95

tgatcacagc gtttaccggc aaa 420

<210> 136

<211> 99 <212> PRT <213> Corynebacterium glutamicum <400> 136 Met His Glu Ser Gly Lys Asn Pro Val Lys Val Val Asp Ser Gln Ala Pro Gln Gly Arg Gly Gly His Ile Gly Gly His Ile Lys Arg Arg Pro Ile Pro Arg Gln Thr Glu Ile Ser Glu Val Arg Arg Tyr Ile Val Met Thr Ala Leu Ala Leu Gly Gly Phe Ala Ile Gly Val Thr Glu Phe Val Ser Met Gly Leu Leu Ser Ala Ile Ala Ser Asp Phe Glu Ile Ser Glu Asp Gln Ala Gly His Ile Ile Thr Ile Tyr Ala Leu Ala Trp Leu Trp Val Pro Arg <210> 137 <211> 379 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (101)..(379) <223> FRXA01984 <400> 137 aggaaatgtc tcacgtcaca accttttgaa aggtggctaa gtacgcacat ttgttgtctg 60 115 caatagtqcc ggtgagggag ctgtccgata ttgtgcttac atg cac gaa tct gga Met His Glu Ser Gly aaa aat cct gtc aag gtt gtc gac tcg cag gca cca caa gga cgc ggt Lys Asn Pro Val Lys Val Val Asp Ser Gln Ala Pro Gln Gly Arg Gly ggg cat atc ggc gga cat atc aaa cgc cgc ccg att cct agg caa acg 211 Gly His Ile Gly Gly His Ile Lys Arg Arg Pro Ile Pro Arg Gln Thr gaa att tcc gag gtt cgt cga tat atc gtc atg act gcc ctc gca ctc 259 Glu Ile Ser Glu Val Arg Arg Tyr Ile Val Met Thr Ala Leu Ala Leu ggt ggc ttc gcc atc ggt gtg acg gaa ttt gtc tcc atg ggt ctg ctc 307

Gly Gly Phe Ala Ile Gly Val Thr Glu Phe Val Ser Met Gly Leu Leu 55 60 65

age geg ate gee tee gae ttt gag ate tee gaa gae eaa gee gga eae 355 Ser Ala Ile Ala Ser Asp Phe Glu Ile Ser Glu Asp Gln Ala Gly His 70 75 80 85

atc atc acc atc tac gcc ctc gcg Ile Ile Thr Ile Tyr Ala Leu Ala 90 379

<210> 138

<211> 93

<212> PRT

<213> Corynebacterium glutamicum

<400> 138

Met His Glu Ser Gly Lys Asn Pro Val Lys Val Val Asp Ser Gln Ala 1 5 10 15

Pro Gln Gly Arg Gly Gly His Ile Gly Gly His Ile Lys Arg Arg Pro 20 25 30

Ile Pro Arg Gln Thr Glu Ile Ser Glu Val Arg Arg Tyr Ile Val Met
35 40 45

Thr Ala Leu Ala Leu Gly Gly Phe Ala Ile Gly Val Thr Glu Phe Val 50 55 60

Ser Met Gly Leu Leu Ser Ala Ile Ala Ser Asp Phe Glu Ile Ser Glu 65 70 75 80

Asp Gln Ala Gly His Ile Ile Thr Ile Tyr Ala Leu Ala 85 90

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<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (101)..(712)

<223> RXA00109

<400> 139

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cggcgaaaag gaagtttcgc ccatctatga gaggttgaat gtg gct tca gag aag 115 Val Ala Ser Glu Lys 1

aat cta aaa ttg cgt acc ttg gcg gca gct gct ggg gtg ttg ggc gtt 163 Asn Leu Lys Leu Arg Thr Leu Ala Ala Ala Ala Gly Val Leu Gly Val 10 15 20

			Met				Glr					Asp	gtg Val	211
	gat Asp 40	Ser				Gly							ccg Pro	259
	att Ile													307
Val	gca Ala													355
	cag Gln													403
	acg Thr				Tyr									451
	ggt Gly 120													499
	gaa Glu													547
	acc Thr													595
	gat Asp					Pro		-				_	_	643
	gtg Val				Val .					Val				691
Lys	aat Asn 200				taag	aggg	tt t	attc	acca	t ga	a			735

<210> 140

<211> 204

<212> PRT

<213> Corynebacterium glutamicum

<400> 140

Val Ala Ser Glu Lys Asn Leu Lys Leu Arg Thr Leu Ala Ala Ala Ala

Gly Val Leu Gly Val Gly Ala Met Ser Met Leu Val Ala Pro Gln Ala 25

Ala Ala His Asp Val Val Val Asp Ser Asn Pro Glu Asn Gly Ser Val

Val Asp Glu Phe Pro Glu Thr Ile Glu Leu Glu Phe Ser Gly Ile Pro

Gln Asp Leu Phe Thr Thr Val Ala Leu Ser Asn Ala Asp Ser Gly Glu

Val Leu Thr Ser Gly Thr Pro Gln Leu Glu Gly Gln His Leu Ser Tyr 90

Glu Val Pro Ser Asp Val Gln Thr Gly Ala Gly Asn Tyr Ile Leu Gly

Phe Gln Ile Thr Ser Ser Asp Gly His Ala Thr Lys Gly Ser Ile Ser

Phe Glu Val Thr Gly Ser Ala Glu Thr Thr Thr Glu Thr Thr Ala Glu

Thr Thr Glu Ser Ala Ala Thr Thr Asp Thr Ser Glu Thr Thr Glu 155

Ala Glu Thr Thr Glu Thr Ala Asp Glu Thr Ser Gly Ile Pro Ala Pro

Trp Asn Trp Val Leu Ser Ile Val Ala Val Leu Val Val Ala Ser Ala

Ile Val Met Met Ile Ala Lys Asn Arg Asn Gln Lys 200

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<212> DNA

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<220>

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cqqcgaaaaq gaagtttcgc ccatctatga gaggttgaat gtg gct tca gag aag Val Ala Ser Glu Lys

aat cta aaa ttg cgt acc ttg gcg gca gct gct ggg gtg ttg ggc gtt

age ate gtg geg gtg ctt gtt gtt gea agt gee ate gte atg atg att

Ser Ile Val Ala Val Leu Val Val Ala Ser Ala Ile Val Met Met Ile 185 190 195

gca aag aat cgt aac cag aaa taagagggtt tattcaccat gaa

<210> 142 <211> 204 <212> PRT <213> Corynebacterium glutamicum

Ala Lys Asn Arg Asn Gln Lys

200

691

735

WO 01/00804 <400> 142 130 165

<400> 142
Val Ala Ser Glu Lys Asn Leu Lys Leu Arg Thr Leu Ala Ala Ala
1 5 10 15

Gly Val Leu Gly Val Gly Ala Met Ser Met Leu Val Ala Pro Gln Ala 20 25 30

Ala Ala His Asp Val Val Val Asp Ser Asn Pro Glu Asn Gly Ser Val
35 40 45

Val Asp Glu Phe Pro Glu Thr Ile Glu Leu Glu Phe Ser Gly Ile Pro 50 55 60

Gln Asp Leu Phe Thr Thr Val Ala Leu Ser Asn Ala Asp Ser Gly Glu 65 70 75 80

Val Leu Thr Ser Gly Thr Pro Gln Leu Glu Gly Gln His Leu Ser Tyr 85 90 95

Glu Val Pro Ser Asp Val Gln Thr Gly Ala Gly Asn Tyr Ile Leu Gly
100 105 110

Phe Gln Ile Thr Ser Ser Asp Gly His Ala Thr Lys Gly Ser Ile Ser 115 120 125

Phe Glu Val Thr Gly Ser Ala Glu Thr Thr Thr Glu Thr Thr Ala Glu 130 135 140

Thr Thr Glu Ser Ala Ala Thr Thr Asp Thr Ser Glu Thr Thr Glu 145 150 155 160

Ala Glu Thr Thr Glu Thr Ala Asp Glu Thr Ser Gly Ile Pro Ala Pro 165 170 175

Trp Asn Trp Val Leu Ser Ile Val Ala Val Leu Val Val Ala Ser Ala 180 185 190

Ile Val Met Met Ile Ala Lys Asn Arg Asn Gln Lys 195 200

<210> 143

<211> 864

<212> DNA

<213> Corynebacterium glutamicum

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<221> CDS

<222> (101)..(841)

<223> RXA00996

<400> 143

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acctctatct tgcacctgat ctggcgtaga ctcataagtt atg agc acc gta acg 115

Met Ser Thr Val Thr

1 5

gca Ala	gtg Val	cag Gln	gtc Val	aac Asn 10	Gly	cta Leu	aaa Lys	gtt Val	tcc Ser 15	Ile	tcg Ser	tcc Ser	ggt Gly	ttt Phe 20	tca Ser	163
cgc Arg	aag Lys	aaa Lys	aca Thr 25	Lys	acg Thr	atc	ttg Leu	cat His 30	Asp	ctc Leu	gat Asp	ttc Phe	acc Thr 35	gta Val	gag Glu	211
			Ile										Gly	aag Lys		259
act Thr	ttg Leu 55	Met	cgc Arg	gcg Ala	att Ile	gtg Val 60	gga Gly	gtg Val	caa Gln	aac Asn	ttc Phe 65	gac Asp	Gly	acc Thr	ctt Leu	307
gag Glu 70	gtg Val	ttt Phe	gat Asp	cag Gln	ccc Pro 75	gca Ala	ggt Gly	gct Ala	gcc Ala	tct Ser 80	ctg Leu	cgc Arg	G] À ààà	aaa Lys	atc Ile 85	355
ggc Gly	tat Tyr	gtc Val	acc Thr	caa Gln 90	aac Asn	gcc Ala	agc Ser	gta Val	tat Tyr 95	cac His	gat Asp	ctg Leu	tcg Ser	gtg Val 100	ata	403
														act Thr		451
cgc Arg	acc Thr	ccg Pro 120	gaa Glu	aag Lys	att Ile	ctg Leu	gag Glu 125	gtc Val	tta Leu	gac Asp	atc Ile	gca Ala 130	gat Asp	ctt Leu	gct Ala	499
caa Gln	cgc Arg 135	caa Gln	gta Val	tca Ser	aca Thr	cta Leu 140	tct Ser	ggt Gly	ggg Gly	cag Gln	cgc Arg 145	ggc Gly	cga Arg	gtc Val	tcc Ser	547
														gat Asp		595
												_	_	gaa Glu 180		643
ttc Phe	acc Thr	acc Thr	atc Ile 185	gca Ala	aaa Lys	gca Ala	ggt Gly	gct Ala 190	gga Gly	gtg Val	gtt Val	atc Ile	tcc Ser 195	agt Ser	cac His	691
gtg Val	ttg Leu	gag Glu 200	gaa Glu	gcc Ala	gcg Ala	cgg Arg	tgc Cys 205	gac Asp	aac Asn	ctc Leu	att Ile	ttg Leu 210	ttg Leu	cgt Arg	gat Asp	739
ggt Gly	cgg Arg 215	atc Ile	atc Ile	tgg Trp	Arg	gga Gly 220	aca Thr	ccc Pro	aca Thr	cgc Arg	ctt Leu 225	cta Leu	gaa Glu	gat Asp	aca Thr	787

WO 01/00804 PCT/IB00/00922

ggc aaa agc tca tac gaa gat gct ttc ttg gct gcc att gac ggg gta Gly Lys Ser Ser Tyr Glu Asp Ala Phe Leu Ala Ala Ile Asp Gly Val 230 245

agg tca tgaaccctca ctatctgctt gcc Arg Ser

864

835

<210> 144

<211> 247

<212> PRT

<213> Corynebacterium glutamicum

<400> 144

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Ser Ser Gly Phe Ser Arg Lys Lys Thr Lys Thr Ile Leu His Asp Leu 20 25 30

Asp Phe Thr Val Glu Thr Gly Lys Ile Thr Gly Leu Leu Gly Pro Ser 35 40 45

Gly Ser Gly Lys Thr Thr Leu Met Arg Ala Ile Val Gly Val Gln Asn 50 55 60

Phe Asp Gly Thr Leu Glu Val Phe Asp Gln Pro Ala Gly Ala Ala Ser 65 70 75 80

Leu Arg Gly Lys Ile Gly Tyr Val Thr Gln Asn Ala Ser Val Tyr His
85 90 95

Asp Leu Ser Val Ile Glu Asn Leu Lys Tyr Phe Gly Ala Leu Ala Lys 100 105 110

Gly Thr Ser Thr Pro Arg Thr Pro Glu Lys Ile Leu Glu Val Leu Asp 115 120 125

Ile Ala Asp Leu Ala Gln Arg Gln Val Ser Thr Leu Ser Gly Gln 130 135 140

Arg Gly Arg Val Ser Leu Gly Cys Ala Leu Ile Ala Ser Pro Glu Leu 145 150 155 160

Leu Val Met Asp Glu Pro Thr Val Gly Leu Asp Pro Ile Thr Arg Gln 165 170 175

Ala Leu Trp Glu Glu Phe Thr Thr Ile Ala Lys Ala Gly Ala Gly Val 180 185 190

Val Ile Ser Ser His Val Leu Glu Glu Ala Ala Arg Cys Asp Asn Leu 195 200 205

Ile Leu Leu Arg Asp Gly Arg Ile Ile Trp Arg Gly Thr Pro Thr Arg 210 215 220 WO 01/00804 PCT/IB00/00922

Leu Leu Glu Asp Thr Gly Lys Ser Ser Tyr Glu Asp Ala Phe Leu Ala 225 230 235 240

Ala Ile Asp Gly Val Arg Ser 245

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Phe	2 Asr 135		l Pro	o Se:	r Val	1 Se:		a Sei	r Gl	y Ala	a Ile 145	_	· Val	Glü	Lys	
	, ĞÎŞ					g Gl					e Lys				ggc Gly 165	595
					s Glu					Ala					ctc Leu	643
				Asp	-				Let		_		-	Leu	acc Thr	691
			Туг					Trp					Tyr		gaa Glu	739
		Leu					Lys					Phe			gaa Glu	787
								gag Glu			Lys				gct Ala 245	835
								ctt Leu		Pro						883
								atg Met 270								931
								cct Pro								979
	Leu	Ala	Pro	His	Ala	Leu	Glu	tcc Ser	Lys	Ile	Asn	Gly				1027
								cgt Arg								1075
								ccc Pro								1123
		Asp						ggt Gly 350								1171
cgc Arg	ccc Pro	gct Ala	ggc Gly	acg Thr	ttg Leu	tct Ser	ggt Gly	ggt Gly	gag Glu	gca Ala	cag Gln	cgc Arg	acc Thr	aag Lys	atg Met	1219

370

ato Ile	cgc Arg 375	His	ttg Leu	g Gly	tct Ser	gca Ala 380	Lev	act Thr	gac Asp	gto Val	acc Thr 385	Tyr	gtt Val	ttt Phe	gat Asp	1267
gaa Glu 390	Pro	acc Thr	gco Ala	ggt Gly	ttg Leu 395	His	gcc Ala	tac Tyr	gac Asp	att Ile 400	Glu	cgc	atg Met	aac Asn	aag Lys 405	1315
					cgc Arg					Thr						1363
				Thr	atc Ile				Asp							1411
					ggt Gly											1459
					agc Ser											1507
					gaa Glu 475											1555
					cga Arg											1603
ccg Pro	ctc Leu	ggc Gly	gtg Val 505	ttc Phe	acg Thr	gcg Ala	att Ile	tcc Ser 510	ggc	gtt Val	gca Ala	ggt Gly	tcg Ser 515	ggt Gly	aag Lys	1651
					gag Glu											1699
					cac His											1747
					tcg Ser 555											1795
					ttc Phe											1843
					tcg Ser		Tyr									1891

gta Val	tct Ser	tcg Ser 600	ccg Pro	tgt Cys	gag Glu	gtg Val	tgc Cys 605	gag Glu	ggc Gly	aag Lys	cgt Arg	ttt Phe 610	gat Asp	gag Glu	tcc Ser	1939
gtg Val	ttg Leu 615	gac Asp	tac Tyr	cac His	ttt Phe	ggt Gly 620	ggc Gly	aag Lys	gac Asp	atc Ile	gca Ala 625	gac Asp	gtg Val	ttg Leu	ggg Gly	1987
ctg Leu 630	tcg Ser	gct Ala	gcc Ala	aat Asn	gcg Ala 635	tat Tyr	gag Glu	ttt Phe	ttc Phe	gcg Ala 640	gcg Ala	aaa Lys	gat Asp	tca Ser	aag Lys 645	2035
att Ile	ttg Leu	cct Pro	gcg Ala	gca Ala 650	aag Lys	atc Ile	gca Ala	aag Lys	agg Arg 655	ctt Leu	gtc Val	gac Asp	gtc Val	ggc Gly 660	ctc Leu	2083
ggc Gly	tac Tyr	atc Ile	acc Thr 665	ctc Leu	ggc Gly	cag Gln	ccg Pro	ctc Leu 670	acc Thr	acg Thr	ttg Leu	tcc Ser	ggc Gly 675	ggt Gly	gaa Glu	2131
cgc Arg	cag Gln	cgt Arg 680	ttg Leu	aag Lys	ctc Leu	gcc Ala	acc Thr 685	cac His	atg Met	gca Ala	gac Asp	aag Lys 690	gcc Ala	acc Thr	acc Thr	2179
ttt Phe	att Ile 695	ttg Leu	gat Asp	gag Glu	ccc Pro	acc Thr 700	aca Thr	ggc Gly	ctg Leu	cac His	ctc Leu 705	gct Ala	gat Asp	gtg Val	aaa Lys	2227
acc Thr 710	ttg Leu	ctg Leu	gat Asp	ctt Leu	ttt Phe 715	gat Asp	caa Gln	ctg Leu	gtt Val	gat Asp 720	gac Asp	ggc Gly	aag Lys	tct Ser	gtc Val 725	2275
atc Ile	gtc Val	atc Ile	gaa Glu	cac His 730	cac His	ctc Leu	ggc Gly	gtg Val	ctc Leu 735	gct Ala	cac His	gct Ala	gac Asp	cac His 740	atc Ile	2323
att Ile	gat Asp	gtc Val	ggc Gly 745	cct Pro	ggt Gly	gca Ala	ggt Gly	tct Ser 750	gat Asp	ggt Gly	ggc Gly	tcg Ser	att Ile 755	gta Val	ttc <u>P</u> he	2371
gag Glu	ggc Gly	agc Ser 760	ccc Pro	gcg Ala	gaa Glu	ctc Leu	atc Ile 765	aaa Lys	act Thr	gat Asp	act Thr	cca Pro 770	aca Thr	gga Gly	cgc Arg	2419
	ctt Leu 775		-		Val		tagt	ttct	ta t	ggaa	aacc	c tg	ıg		•	2463

<210> 146

<211> 780

<212> PRT

<213> Corynebacterium glutamicum

<400> 146

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•

Glu Asn Asn Leu Lys Asn Val Ser Val Arg Ile Pro Lys Arg Arg Leu 20 25 30

Thr Val Phe Thr Gly Val Ser Gly Ser Gly Lys Ser Ser Leu Val Phe 35 40 45

Gly Thr Ile Ala Ala Glu Ser Arg Arg Leu Ile Asn Glu Thr Tyr Ser 50 55 60

Thr Phe Val Gln Gly Phe Met Pro Ser Met Ala Arg Pro Asp Val Asp 65 70 75 80

His Leu Glu Gly Ile Thr Thr Ala Ile Ile Val Asp Gln Glu Gln Met
85 90 95

Gly Ala Asn Pro Arg Ser Thr Val Gly Thr Ala Thr Asp Ala Thr Ala 100 105 110

Met Leu Arg Ile Leu Phe Ser Arg Ile Ala Glu Pro Asn Ala Gly Gly 115 120 125

Pro Gly Ala Tyr Ser Phe Asn Val Pro Ser Val Ser Ala Ser Gly Ala 130 135 140

Ile Thr Val Glu Lys Gly Gly Asn Thr Lys Arg Glu Lys Ala Thr Phe 145 150 155 160

Lys Arg Thr Gly Gly Met Cys Pro Ala Cys Glu Gly Met Gly Arg Ala 165 170 175

Ser Asp Ile Asp Leu Lys Glu Leu Phe Asp Ala Ser Leu Ser Leu Asn 180 . 185 . 190

Asp Gly Ala Leu Thr Ile Pro Gly Tyr Thr Pro Gly Gly Trp Ser Tyr 195 200 205

Arg Met Tyr Ser Glu Ser Gly Leu Phe Asp Ala Ala Lys Pro Ile Bys 210 215 220

Asp Phe Thr Glu Glu Glu Arg His Asn Phe Leu Tyr Leu Glu Pro Thr 225 230 235 240

Lys Met Lys Ile Ala Gly Ile Asn Met Thr Tyr Glu Gly Leu Ile Pro 245 250 255

Arg Ile Gln Lys Ser Met Leu Ser Lys Asp Arg Glu Gly Met Gln Lys 260 265 270

His Ile Arg Ala Phe Val Asp Arg Ala Val Thr Phe Ile Pro Cys Pro 275 280 285

Ala Cys Gly Gly Thr Arg Leu Ala Pro His Ala Leu Glu Ser Lys Ile 290 295 300

Asn Gly Lys Asn Ile Ala Glu Leu Cys Ala Met Glu Val Arg Asp Leu

310

315

320

Ala Lys Trp Ile Lys Thr Val Glu Ala Pro Ser Val Ala Pro Leu Leu 325 330 335

Thr Ala Leu Thr Glu Thr Leu Asp Asn Phe Val Glu Ile Gly Leu Gly 340 345 350

Tyr Ile Gln Leu Asp Arg Pro Ala Gly Thr Leu Ser Gly Glu Ala 355 360 365

Gln Arg Thr Lys Met Ile Arg His Leu Gly Ser Ala Leu Thr Asp Val 370 375 380

Thr Tyr Val Phe Asp Glu Pro Thr Ala Gly Leu His Ala Tyr Asp Ile 385 390 395 400

Glu Arg Met Asn Lys Leu Leu Leu Asp Leu Arg Asp Lys Gly Asn Thr 405 410 415

Val Leu Val Val Glu His Lys Pro Glu Thr Ile Ala Ile Ala Asp His 420 425 430

Val Val Asp Leu Gly Pro Gly Ala Gly Ala Gly Gly Gly Glu Ile Arg 435 440 445

Phe Glu Gly Ser Val Asp Lys Leu Lys Asp Ser Asp Thr Val Thr Gly 450 455 460

Leu His Phe Asn Asp Arg Ala Ser Leu Lys Glu Ser Val Arg Ala Pro 465 470 475 480

His Gly Ala Leu Glu Ile Arg Gly Ala Asp Arg Asn Asn Leu Asn Asn 485 490 495

. Val Asp Val Asp Ile Pro Leu Gly Val Phe Thr Ala Ile Ser Gly Val
500 505 510

Ala Gly Ser Gly Lys Ser Ser Leu Ile His Glu Ile Pro Arg Asp Glu 515 520 525

Ser Val Val Phe Val Asp Gln Thr Ala Ile His Gly Ser Asn Arg Ser 530 535 540

Asn Pro Ala Thr Tyr Thr Gly Met Leu Asp Ser Ile Arg Lys Ala Phe 545 550 555 560

Ala Lys Ala Asn Asp Val Lys Pro Ala Leu Phe Ser Pro Asn Ser Glu 565 570 575

Gly Ala Cys Pro Asn Cys Lys Gly Ala Gly Ser Val Tyr Val Asp Leu
580 585 590

Gly Met Met Ala Gly Val Ser Ser Pro Cys Glu Val Cys Glu Gly Lys 595 600 605

Arg Phe Asp Glu Ser Val Leu Asp Tyr His Phe Gly Gly Lys Asp Ile

610 615 620

Ala Asp Val Leu Gly Leu Ser Ala Ala Asn Ala Tyr Glu Phe Phe Ala 625 635 640

Ala Lys Asp Ser Lys Ile Leu Pro Ala Ala Lys Ile Ala Lys Arg Leu 645 650 655

Val Asp Val Gly Leu Gly Tyr Ile Thr Leu Gly Gln Pro Leu Thr Thr 660 665 670

Leu Ser Gly Glu Arg Gln Arg Leu Lys Leu Ala Thr His Met Ala 675 680 685

Asp Lys Ala Thr Thr Phe Ile Leu Asp Glu Pro Thr Thr Gly Leu His 690 695 700

Leu Ala Asp Val Lys Thr Leu Leu Asp Leu Phe Asp Gln Leu Val Asp 705 710 715 720

Asp Gly Lys Ser Val Ile Val Ile Glu His His Leu Gly Val Leu Ala 725 730 735

His Ala Asp His Ile Ile Asp Val Gly Pro Gly Ala Gly Ser Asp Gly
740 745 750

Gly Ser Ile Val Phe Glu Gly Ser Pro Ala Glu Leu Ile Lys Thr Asp 755 760 765

Thr Pro Thr Gly Arg His Leu Lys Ala Tyr Val Asp 770 775 780

<210> 147

<211> 278

<212> DNA

<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (1)..(255)

<223> FRXA00829

<400> 147

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Leu Asp Glu Pro Thr Thr Gly Leu His Leu Ala Asp Val Lys Thr Leu
1 5 10 15

ctg gat ctt ttt gat caa ctg gtt gat gac ggc aag tct gtc atc gtc 96 Leu Asp Leu Phe Asp Gln Leu Val Asp Asp Gly Lys Ser Val Ile Val 20 25 30

atc gaa cac cac ctc ggc gtg ctc gct cac gct gac cac atc att gat 144
Ile Glu His His Leu Gly Val Leu Ala His Ala Asp His Ile Ile Asp
35 40 45

gtc ggc cct ggt gca ggt tct gat ggt ggc tcg att gta ttc gag ggc 192

WO 01/00804 Val Gly Pro Gly Ala Gly Ser Asp Gly Gly Ser Ile Val Phe Glu Gly 240 age ece geg gaa ete ate aaa act gat act eca aca gga ege eae ett Ser Pro Ala Glu Leu Ile Lys Thr Asp Thr Pro Thr Gly Arg His Leu aaa gct tat gta gat tagtttctta tggaaaaccc tgg 278 Lys Ala Tyr Val Asp 85 <210> 148 <211> 85 <212> PRT <213> Corynebacterium glutamicum <400> 148 Leu Asp Glu Pro Thr Thr Gly Leu His Leu Ala Asp Val Lys Thr Leu Leu Asp Leu Phe Asp Gln Leu Val Asp Asp Gly Lys Ser Val Ile Val Ile Glu His His Leu Gly Val Leu Ala His Ala Asp His Ile Ile Asp Val Gly Pro Gly Ala Gly Ser Asp Gly Gly Ser Ile Val Phe Glu Gly Ser Pro Ala Glu Leu Ile Lys Thr Asp Thr Pro Thr Gly Arg His Leu 65 Lys Ala Tyr Val Asp <210> 149 <211> 1663 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS

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caagcgcgaa caggcctatg caaacggtac gatatgacac atg caa aaa gct gat 115 Met Gln Lys Ala Asp

tcc cat gat tgg att tcg gtc cac ggt gcg aat gaa aac aac ctc aaa 163 Ser His Asp Trp Ile Ser Val His Gly Ala Asn Glu Asn Asn Leu Lys 15 10

aat Asn	gtg Val	tcg Ser	gtg Val	Arg	atc Ile	cct	aaa Lys	agg Arg 30	Arg	ctc Leu	acc	gtg Val	ttc Phe 35	Thr	ggt Gly	211
gtg Val	tcg Ser	gga Gly 40	Ser	ggc	aag Lys	tcc Ser	tcg Ser 45	Leu	gtg Val	ttc Phe	ggc	aca Thr 50	Ile	gct Ala	gcg Ala	259
		Arg			atc Ile		Glu					Phe				307
	Met				gca Ala 75											355
					gtc Val											403
Ser	Thr	Val	Gly 105	Thr	gca Ala	Thr	Asp	Ala 110	Thr	Ala	Met	Leu	Arg 115	Ile	Leu	451
Phe	Ser	Arg 120	Ile	Ala	gaa Glu	Pro	Asn 125	Ala	Gly	Gly	Pro	Gly 130	Ala	Tyr	Ser	499
Phe	Asn 135	Val	Pro	Ser	gtt Val	Ser 140	Ala	Ser	Gly	Ala	Ile 145	Thr	Val	Glu	Lys	547
Gly 150	Gly	Asn	Thr	Lys	cgg Arg 155	Glu	Lys	Ala	Thr	Phe 160	Lys	Arg	Thr	Gly	Gly 165	595
Met	Cys	Pro	Ala	Cys 170	gag Glu	Gly	Met	Gly	Arg 175	Ala	Ser	Asp	Ile	Asp 180	Leu	643
Lys	Glu	Leu	Phe 185	Asp	gcc Ala	Ser	Leu	Ser 190	Leu	Asn	Asp	Gly	Ala 195	Leu	Thr	691
Ile	Pro	Gly 200	Tyr	Thr	cca Pro	Gly	Gly 205	Trp	Ser	Tyr	Arg	Met 210	Tyr	Ser	Glu	739
Ser	Gly 215	Leu	Phe	Asp		Ala 220	Lys	Pro	Ile	Lys	Asp 225	Phe	Thr	Glu	Glu	7 87
				Phe	ctt Leu 235											835

								•									
						r Ty					e Pro					tcc s Ser	883
					s As					Glr					Ala	g ttc a Phe	931 .
				g Āl					Pro					Gĺy		a act	979
			Al					Glu					ıĞİy			atc lle	1027
1		Glu					Glu					Ala	aag Lys			aaa Lys 325	1075
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					Phe								atc				1171
				Gly									cgc Arg 370				1219
													tat Tyr				1267
G													cgc Arg				1315
													tta Leu				1363
													gtg Val				1411
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	φ					Ser							cat His				1507

PCT/IB00/00922

WO 01/00804

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Gly Thr Ile Ala Ala Glu Ser Arg Arg Leu Ile Asn Glu Thr Tyr Ser

Thr Phe Val Gln Gly Phe Met Pro Ser Met Ala Arg Pro Asp Val Asp

His Leu Glu Gly Ile Thr Thr Ala Ile Ile Val Asp Gln Glu Gln Met

Gly Ala Asn Pro Arg Ser Thr Val Gly Thr Ala Thr Asp Ala Thr Ala

Met Leu Arg Ile Leu Phe Ser Arg Ile Ala Glu Pro Asn Ala Gly Gly 115

Pro Gly Ala Tyr Ser Phe Asn Val Pro Ser Val Ser Ala Ser Gly Ala

Ile Thr Val Glu Lys Gly Gly Asn Thr Lys Arg Glu Lys Ala Thr Phe 145

Lys Arg Thr Gly Gly Met Cys Pro Ala Cys Glu Gly Met Gly Arg Ala

Ser Asp Ile Asp Leu Lys Glu Leu Phe Asp Ala Ser Leu Ser Leu Asn 185

- Asp Gly Ala Leu Thr Ile Pro Gly Tyr Thr Pro Gly Gly Tyr Pro Gly 205 Try Ser Tyr 210 Thr 210 Ser Gly Leu Phe Asp Ala Ala Lys Pro Ile Lys 225 Phe Thr Glu Glu Glu Arg His Asn Phe Leu Tyr Glu Gly Leu Glu Pro 240 Lys Met Lys Ile Ala Gly Ile Asn Met Thr Tyr Glu Gly Leu Ile Pro 255 Arg Ile Arg Ala Phe Val Asp Arg Ala Val Thr Phe Ile Pro 285 Pro Ala Cys Gly Gly Thr Arg Leu Ala Glu Leu Cys Ala Met Glu Glu Gly Leu Ile Asp Leu 300 Gly Lys Asp Ile Ala Glu Leu Cys Ala Met Glu Val Arg Asp Leu 300 Gly Lys Asp Leu 310 Chy Ser Lys Ile
- Ala Lys Trp Ile Lys Thr Val Glu Ala Pro Ser Val Ala Pro Leu Leu 325 330 335
- Thr Ala Leu Thr Glu Thr Leu Asp Asn Phe Val Glu Ile Gly Leu Gly

- Tyr Ile Gln Leu Asp Arg Pro Ala Gly Thr Leu Ser Gly Gly Glu Ala
- Gln Arg Thr Lys Met Ile Arg His Leu Gly Ser Ala Leu Thr Asp Val
- Thr Tyr Val Phe Asp Glu Pro Thr Ala Gly Leu His Ala Tyr Asp Ile 385 390 395 400
- Glu Arg Met Asn Lys Leu Leu Leu Asp Leu Arg Asp Lys Gly Asn Thr 405 410 415
- Val Leu Val Val Glu His Lys Pro Glu Thr Ile Ala Ile Ala Asp His
 420 425 430
- Val Val Asp Leu Gly Pro Gly Ala Gly Ala Gly Gly Glu Ile Arg 435 440 445
- Phe Glu Gly Ser Val Asp Lys Leu Lys Asp Ser Asp Thr Val Thr Gly 450 455 460
- Leu His Phe Asn Asp Arg Ala Ser Leu Lys Glu Ser Val Arg Ala Pro 465 470 475 480
- His Gly Ala Leu Glu Ile Arg Gly Ala Asp Arg Asn Asn Leu Asn Asn 485 490 495

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Ala Gly Ser Gly Lys Ser Ser Leu Ile 515 520

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<400> 151

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ctg ctt gcc acg gtc aaa cga gtc ctg ctg cag ctg aaa gcc gat aaa 163 Leu Leu Ala Thr Val Lys Arg Val Leu Leu Gln Leu Lys Ala Asp Lys 10 15 20

cgt tcc atc gcg ctg att ctt cta gca ccc gtg gcg ttg atg tcg ctg 211
Arg Ser Ile Ala Leu Ile Leu Leu Ala Pro Val Ala Leu Met Ser Leu
25 30 35

ttt tat tac atg tat tcc tcc aca ccg gca ggc acc cag ctg ttt aag 259
Phe Tyr Tyr Met Tyr Ser Ser Thr Pro Ala Gly Thr Gln Leu Phe Lys
40 45 50

acc att tcc acg gtc atg atc gca gtg ttc ccc ttg atg ctc atg ttt 307
Thr Ile Ser Thr Val Met Ile Ala Val Phe Pro Leu Met Leu Met Phe
55 60 65

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gag cgc ttg tgg acc acg aac att cac cgc gtt gat ttg atc ggt ggc 403 Glu Arg Leu Trp Thr Thr Asn Ile His Arg Val Asp Leu Ile Gly Gly 90 95 100

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Tyr Gly Val Ala Phe Gly Ile Met Ala Val Ala Gln Ser Leu Leu Met
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Thr Arg

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Ala Leu Met Ser Leu Phe Tyr Tyr Met Tyr Ser Ser Thr Pro Ala Gly
35 40 45

Thr Gln Leu Phe Lys Thr Ile Ser Thr Val Met Ile Ala Val Phe Pro 50 55 60

Leu Met Leu Met Phe Leu Met Thr Ser Val Thr Met Gln Arg Glu Arg 65 70 75 80

Asn Ala Gly Thr Leu Glu Arg Leu Trp Thr Thr Asn Ile His Arg Val 85 90 95 Thr Glu Ser Glu Trp Trp Ile Ser Thr Leu Ile Ala Ala Ile Thr Gly 135

Leu Ile Gly Val Ser Leu Gly Leu Leu Ser Ser Ala Phe Ala Ser Thr 150 155 160

Glu Phe Gln Ala Ile Gln Thr Leu Pro Leu Leu Ile Leu Pro Gln Phe

Leu Leu Cys Gly Leu Leu Ile Pro Arg Asp Asp Leu Pro Asp Val Leu 185

Arg Trp Val Ser Asn Val Leu Pro Leu Ser Tyr Ala Val Asp Ala Ala

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<223> RXN00803

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ctt aac atg tct gac atg gtg gcg aac aaa cgg gca cag cgt aaa gtc 163 Leu Asn Met Ser Asp Met Val Ala Asn Lys Arg Ala Gln Arg Lys Val

tgg cta gcg gta gct tta tcg gtc ttt acg gtc gcg tgg ggt ggc aat 211 Trp Leu Ala Val Ala Leu Ser Val Phe Thr Val Ala Trp Gly Gly Asn

gaa tto act ccc ttg ctg gtg ttt tac cga ggt gaa ggg ttc ttt agc

Glu Phe Thr Pro Leu Leu Val Phe Tyr Arg Gly Glu Gly Phe The Ser 45 aac ctg ttc atc gac ctt ttg ctg gtg ttt tat gcc atc gga gta gcg 307 Asn Leu Phe Ile Asp Leu Leu Leu Val Phe Tyr Ala Ile Gly Val Ala gta ggt ttg ctg gca gct ggt cct tta tct gac cgc tat ggc cga cgt 355 Val Gly Leu Leu Ala Ala Gly Pro Leu Ser Asp Arg Tyr Gly Arg Arg gcc gtc atg ttg cct gcg cca ttg atc gcg atc ttg ggt tcc gcg ttg 403 Ala Val Met Leu Pro Ala Pro Leu Ile Ala Ile Leu Gly Ser Ala Leu att gcc tcg ggt gaa gaa acc gcc atc ctg att gcc att ggt cga gtg 451 Ile Ala Ser Gly Glu Glu Thr Ala Ile Leu Ile Ala Ile Gly Arg Val 105 ctg tcg gga att tcg gtg ggc atg gtg atg aca gcg gga ggt tcc tgg 499 Leu Ser Gly Ile Ser Val Gly Met Val Met Thr Ala Gly Gly Ser Trp 120 125 att aag gag ctt tca tcg tcg cgg ttt gag cca ggg gtg aaa acc agt 547 Ile Lys Glu Leu Ser Ser Ser Arg Phe Glu Pro Gly Val Lys Thr Ser 135 gct ggt gca aaa cgc gca tcg atg tct ttg acc ggt ggt ttt gcg ctc 595 Ala Gly Ala Lys Arg Ala Ser Met Ser Leu Thr Gly Gly Phe Ala Leu 155 ggc cca gcg ctt gct ggt gtg atg gca cag tgg ctg cca cta cct gga Gly Pro Ala Leu Ala Gly Val Met Ala Gln Trp Leu Pro Leu Pro Gly 175 cag ttg gca tat gtt ttg cac att att ctc act ctg att ttg ttc ccg 691 Gln Leu Ala Tyr Val Leu His Ile Ile Leu Thr Leu Ile Leu Phe Pro 185 190 ttg ctt att aca gcg ccg gaa act cgt caa tca gcg cac ctg aaa act 739 Leu Leu Ile Thr Ala Pro Glu Thr Arg Gln Ser Ala His Leu Lys Thr aag gga tca ttc tgg tca gat gtg ctt gtg cca tct gca cta gac aag 787 Lys Gly Ser Phe Trp Ser Asp Val Leu Val Pro Ser Ala Leu Asp Lys cga ttc ttg ttt gtg gtt gct cca att gga ccg tgg gtt ttc ggt gcg 835 Arg Phe Leu Phe Val Val Ala Pro Ile Gly Pro Trp Val Phe Gly Ala gcc ttc act gcc tac gca gtt ttg ccg tcg cag ctg cgt gac atg gtt 883 Ala Phe Thr Ala Tyr Ala Val Leu Pro Ser Gln Leu Arg Asp Met Val tct gca ccc gtt gcg tat tct gcg ctg atc gct ttg gtt acc tta ggt Ser Ala Pro Val Ala Tyr Ser Ala Leu Ile Ala Leu Val Thr Leu Gly

265 270

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aaa act cgc ggg ccg att ttg gcc atg ttc gtc aca gtc atc ggc atg
Lys Thr Arg Gly Pro Ile Leu Ala Met Phe Val Thr Val Ile Gly Met
295 300 305

atc ggc gcg gtg atc gtg gtg atg aac cct cat cca tgg tgg gcg cta 1075 Ile Gly Ala Val Ile Val Val Met Asn Pro His Pro Trp Trp Ala Leu 310 325

gtt ggc tgc atg gcc ctc ggc ctg tct tat ggc ctg tgt atg ttc atg
Val Gly Cys Met Ala Leu Gly Leu Ser Tyr Gly Leu Cys Met Phe Met
330
335
340

ggg ttg gcg gaa act caa aac att gct cca cct att gat atg gca ggc 1171 Gly Leu Ala Glu Thr Gln Asn Ile Ala Pro Pro Ile Asp Met Ala Gly 345 350 355

ctg acg ggt att ttc tac tgc ctg acg tac gta ggt atg gtc ttt cca 1219
Leu Thr Gly Ile Phe Tyr Cys Leu Thr Tyr Val Gly Met Val Phe Pro
360 365 370

gcc ttg atg acc tgg ttg aat caa tgg ctc agt tac ccg ttc atg ctg
Ala Leu Met Thr Trp Leu Asn Gln Trp Leu Ser Tyr Pro Phe Met Leu
375 380 385

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<213> Corynebacterium glutamicum

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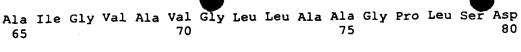
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Ala Trp Gly Gly Asn Glu Phe Thr Pro Leu Leu Val Phe Tyr Arg Gly 35 40 45

Glu Gly Phe Phe Ser Asn Leu Phe Ile Asp Leu Leu Leu Val Phe Tyr 50 55 60



Arg Tyr Gly Arg Arg Ala Val Met Leu Pro Ala Pro Leu Ile Ala Ile 85 90 95

Leu Gly Ser Ala Leu Ile Ala Ser Gly Glu Glu Thr Ala Ile Leu Ile 100 105 110

Ala Ile Gly Arg Val Leu Ser Gly Ile Ser Val Gly Met Val Met Thr 115 120 125

Ala Gly Gly Ser Trp Ile Lys Glu Leu Ser Ser Ser Arg Phe Glu Pro 130 135 140

Gly Val Lys Thr Ser Ala Gly Ala Lys Arg Ala Ser Met Ser Leu Thr 145 150 155 160

Gly Gly Phe Ala Leu Gly Pro Ala Leu Ala Gly Val Met Ala Gln Trp 165 170 175

Leu Pro Leu Pro Gly Gln Leu Ala Tyr Val Leu His Ile Ile Leu Thr 180 185 190

Leu Ile Leu Phe Pro Leu Leu Ile Thr Ala Pro Glu Thr Arg Gln Ser 195 200 205

Ala His Leu Lys Thr Lys Gly Ser Phe Trp Ser Asp Val Leu Val Pro 210 215 220

Ser Ala Leu Asp Lys Arg Phe Leu Phe Val Val Ala Pro Ile Gly Pro 225 230 235 240

Trp Val Phe Gly Ala Ala Phe Thr Ala Tyr Ala Val Leu Pro Ser Gln 245 250 255

Leu Arg Asp Met Val Ser Ala Pro Val Ala Tyr Ser Ala Leu Ile Ala 260 265 270

Leu Val Thr Leu Gly Ser Gly Phe Gly Ile Gln Gln Phe Gly Pro Gln 275 280 285

Ile Met Gly Thr Ser Lys Thr Arg Gly Pro Ile Leu Ala Met Phe Val 290 295 300

Thr Val Ile Gly Met Ile Gly Ala Val Ile Val Val Met Asn Pro His 305 310 315 320

Pro Trp Trp Ala Leu Val Gly Cys Met Ala Leu Gly Leu Ser Tyr Gly 325 330 335

Leu Cys Met Phe Met Gly Leu Ala Glu Thr Gln Asn Ile Ala Pro Pro 340 345 350

Ile Asp Met Ala Gly Leu Thr Gly Ile Phe Tyr Cys Leu Thr Tyr Val 355 360 365

Gly Met Val Phe Pro Ala Leu Met Thr Trp Leu Asn Gln Trp Leu Ser 370 375 380

Tyr Pro Phe Met Leu Gly Phe Gly Ala Val Met Ala Thr Ile Cys Leu 385 390 395 400

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Met Gly Val Ser Ala

1 5

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Trp Leu Ala Val Ala Leu Ser Val Phe Thr Val Ala Trp Gly Gly Asn
25 30 35

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Glu Phe Thr Pro Leu Leu Val Phe Tyr Arg Gly Glu Gly Phe Phe Ser

aac ctg ttc atc gac ctt ttg ctg gtg ttt tat gcc atc gga gta gcg 307 Asn Leu Phe Ile Asp Leu Leu Val Phe Tyr Ala Ile Gly Val Ala

gta ggt ttg ctg gca gct ggt cct tta tct gac cgc tat ggc cga cgt 355 Val Gly Leu Leu Ala Ala Gly Pro Leu Ser Asp Arg Tyr Gly Arg Arg 70 85

gcc gtc atg ttg cct gcg cca ttg atc gcg atc ttg ggt tcc gcg ttg 403 Ala Val Met Leu Pro Ala Pro Leu Ile Ala Ile Leu Gly Ser Ala Leu 90 95 100

att gcc tcg ggt gaa gaa acc gcc atc ctg att gcc att ggt cga gtg 451 Ile Ala Ser Gly Glu Glu Thr Ala Ile Leu Ile Ala Ile Gly Arg Val 105 110 115

ctg tcg gga att tcg gtg ggc atg gtg atg aca gcg gga ggt tcc tgg 499 Leu Ser Gly Ile Ser Val Gly Met Val Met Thr Ala Gly Gly Ser Trp

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35 40 45

Glu Gly Phe Phe Ser Asn Leu Phe Ile Asp Leu Leu Val Phe Tyr
50 60

Ala Ile Gly Val Ala Val Gly Leu Leu Ala Ala Gly Pro Leu Ser Asp
65 70 75 80

Arg Tyr Gly Arg Arg Ala Val Met Leu Pro Ala Pro Leu Ile Ala Ile 85 90 95

Leu Gly Ser Ala Leu Ile Ala Ser Gly Glu Glu Thr Ala Ile Leu Ile 100 105 110

Ala Ile Gly Arg Val Leu Ser Gly Ile Ser Val Gly Met Val Met Thr 115 120 125

Ala Gly Gly Ser Trp Ile Lys Glu Leu Ser Ser Ser Arg Phe Glu Pro 130 135 140

Gly Val Lys Thr Ser Ala Gly Ala Lys Arg Ala Ser Met Ser Leu Thr

155

160

Gly Gly Phe Ala Leu Gly Pro Ala Leu Ala Gly Val Met Ala Gln Trp 165 170 175

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Leu Ile Leu Phe Pro Leu Leu Ile Thr 195 200

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Leu Gln Asp Thr Ile

1 5

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Ile Met Ala Gly Leu Phe Ile Gln Pro Lys Asn Thr Ala Val Asn Val
25 30 35

aag cga ttt gat cgg cca ggt ttc ctc ggc gca atg ctg gtg atg gtg 259 Lys Arg Phe Asp Arg Pro Gly Phe Leu Gly Ala Met Leu Val Met Val 40 45 50

gcg caa gcc gtg att gcg gag tta att tgc agc aga agt ccg gcc gca 307 Ala Gln Ala Val Ile Ala Glu Leu Ile Cys Ser Arg Ser Pro Ala Ala 55 60 65

ctt act atc tgt gca tgc ctc gtc tta agt gct gcg gtg gta tgc ggt
Leu Thr Ile Cys Ala Cys Leu Val Leu Ser Ala Ala Val Val Cys Gly
70 75 80 85

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atc atg cgc atc cca ggt ttc cga gtg ggt aat tcc tcc gga agt atc 451
Ile Met Arg Ile Pro Gly Phe Arg Val Gly Asn Ser Ser Gly Ser Ile
105 110 115

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		Ala		ggg Gly			Ala								547
				ggc Gly		Val					Phe				595
				aat Asn 170											643
				ttg Leu								Ala			691
				gtg Val											739
				gcc Ala											787
-			_	aac Asn	_					_		-			835
				ggt Gly 250											883
				tgg Trp			Pro								931
cct Pro	Leu					Ser					Gly				979
ttt Phe				taga	aacc	ca c	ttct	gaaa	g gt	a				•	1014
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Arg Ser Pro Ala Ala Leu Thr Ile Cys Ala Cys Leu Val Leu Ser Ala 65 70 75 80

Ala Val Val Cys Gly Phe Val Val Arg Trp Leu Arg Val Pro Gly Arg 85 90 95

Leu Phe Asp Leu Ser Ile Met Arg Ile Pro Gly Phe Arg Val Gly Asn 100 105 110

Ser Ser Gly Ser Ile Tyr Arg Leu Val Ile Thr Ala Ala Pro Phe Met 115 120 125

Phe Thr Leu Leu Phe Gln Val Ala Phe Gly Trp Ser Ala Thr Leu Ala 130 135 140

Gly Ala Met Val Val Ala Leu Phe Ala Gly Asn Val Ala Ile Lys Pro 145 150 155 160

Phe Thr Thr Pro Ile Ile Lys Arg Trp Asn Phe Lys Pro Val Leu Val 165 170 175

Phe Ser Asn Ala Ala Gly Ala Leu Val Leu Ala Thr Phe Leu Phe Val 180 185 190

Arg Ala Asp Thr Pro Leu Val Leu Ile Val Leu Leu Leu Phe Val Ser 195 200 205

Gly Ala Leu Arg Ser Leu Gly Phe Ser Ala Tyr Asn Thr Leu Gln Phe 210 215 220

Val Asp Ile Ser Pro Glu Gln Thr Ser Asn Ala Asn Val Leu Ser Ala 225 230 235 240

Thr Leu His Gln Leu Gly Met Ser Leu Gly Ile Ala Val Ala Val Ile 245 250 255

Ala Met Ser Leu Ala Pro Thr Ala Asn Trp Ala Phe Pro Leu Ala Ala 260 265 270

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Gly Gly Ala Arg Ala Phe Ser Ser Ser 290 295

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gac	cgtc	ttt	cacc	cttt	ca t	ctga	ttgg	a ca	tcga	cgcc	atg Met 1	cgc Arg	aat Asn	gat Asp	cgg Arg 5	115
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gaa Glu	atc Ile	ctc Leu	gac Asp 25	ggc Gly	acc Thr	atc Ile	ctg Leu	aca Thr 30	acc Thr	gca Ala	gtg Val	cca Pro	gct Ala 35	att Ile	gct Ala	211
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tac Tyr	ttg Leu 55	gca Ala	gcc Ala	gca Ala	gca Ala	gct Ala 60	ggc Gly	att Ile	ccg Pro	ctg Leu	cag Gln 65	ggt Gly	ggc Gly			301
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Gly	Ala	Leu	Phe 20	Leu	Glu	Ile	Leu	Asp 25	Gly	Thr	Ile	Leu	Thr 30	Thr	Ala	
Val	Pro	Ala 35	Ile	Ala	Arg	Asp	Phe 40	Gly	Ile	Asp	Ala	Val 45	Asp	Val	Ser	
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Gln Gly Gly 65 WO 01/00804 PCT/IB00/00922

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PCT/IB00/00922 WO 01/00804 643 gtt gcc ctc tcg ctg atc gcg gtg gtt gtg gga ttt gcg ctt ggc gat Val Ala Leu Ser Leu Ile Ala Val Val Gly Phe Ala Leu Gly Asp 691 gcc cgc agc acc ccg agc gca ctt ggc gca tcc agc gga atc aaa cac Ala Arg Ser Thr Pro Ser Ala Leu Gly Ala Ser Ser Gly Ile Lys His 185 190 739 gaa cga agc atg aaa aag gcc ctc gcg gtg tcc ttg ccg atg gca att Glu Arg Ser Met Lys Lys Ala Leu Ala Val Ser Leu Pro Met Ala Ile 205 787 tgg gtg ttc agc tgc atc acc tcc ctg atc gtg atg tcc gcg cgc Trp Val Phe Ser Cys Ile Thr Thr Ser Leu Ile Val Met Ser Ala Arg 215 atc gac tcc acc ttc ggc aac gcc att ctt ctc ccc gga atc ggc gcg 835 Ile Asp Ser Thr Phe Gly Asn Ala Ile Leu Leu Pro Gly Ile Gly Ala 235 230 geg atc gcc ttc agc gca ggc ctg atc gca caa ttt tta ggt agg aaa 883 250 260 tte geg tgg ggt egt gge tee gga ate gtg gge geg etg tgt gee ete 931 265 979 280 1027 295 300

Ala Ile Ala Phe Ser Ala Gly Leu Ile Ala Gln Phe Leu Gly Arg Lys Phe Ala Trp Gly Arg Gly Ser Gly Ile Val Gly Ala Leu Cys Ala Leu gcq ggt ttt gcg ctg gca gct ttt ggt ggc gac tcc att cca gtg tgg Ala Gly Phe Ala Leu Ala Ala Phe Gly Gly Asp Ser Ile Pro Val Trp ctt ttc qtt atc gcc tcg atc ctg ttc ggc acc gca tat ggc ctc tgc Leu Phe Val Ile Ala Ser Ile Leu Phe Gly Thr Ala Tyr Gly Leu Cys ctq cqc gaa ggc ctc ctc agc atc gaa act tac acg cca ctc aac cga 1075 Leu Arg Glu Gly Leu Leu Ser Ile Glu Thr Tyr Thr Pro Leu Asn Arg 310 cgt ggc acc ggc atc ggc atc tat tat gtg ttc acg tat ttg gga ttc 1123 Arg Gly Thr Gly Ile Gly Ile Tyr Tyr Val Phe Thr Tyr Leu Gly Phe ggg ctg cca gtg ctt ctc gac gcc ctc ctc ccg cac ctt ggc gcc tcc 1171 Gly Leu Pro Val Leu Leu Asp Ala Leu Leu Pro His Leu Gly Ala Ser 345 1219 att ccg ctg tac gcg ctg gcg ctc gcc ctt ggc tcc gca gta atc Ile Pro Leu Tyr Ala Leu Ala Ala Leu Ala Leu Gly Ser Ala Val Ile 360 365 cgc ggc gta caa atc aag cgc ggg tat gtg gtt tagatttcta cctacgacct 1272 Arg Gly Val Gln Ile Lys Arg Gly Tyr Val Val 375 380

1275 gaa

<210> 162 <211> 384 <212> PRT <213> Corynebacterium glutamicum

<400> 162

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Leu Ile Arg Glu Gln Leu Asp Val Ser Ser Val Leu Val Asn Gly Ala 35 40 45

Phe Gly Ile Tyr Ala Leu Gly Leu Leu Pro Ser Leu Leu Ala Gly Gly 50 60

Val Leu Ala Asp Arg Phe Gly Ala Arg Met Val Val Leu Thr Gly Gly 65 70 75 80

Val Leu Ser Ala Leu Gly Asn Leu Ser Leu Leu Ala Phe His Asp Gly 85 90 95

Pro Ser Leu Leu Val Gly Arg Phe Ile Val Gly Leu Gly Val Gly Leu 100 105 110

Val Val Ser Ala Gly Thr Ala Trp Ala Gly Arg Leu Arg Gly Ala Ser 115 120 125

Gly Val Thr Leu Ala Gly Ile Ile Leu Thr Ala Gly Phe Met Met Gly 130 135 140

Pro Ile Val Thr Ser Gly Leu Gly Met Ala Ser Thr Ser Ile Ile Thr 145 150 155 160

Pro Phe Ala Ile Ser Val Ala Leu Ser Leu Ile Ala Val Val Gly 165 170 175

Phe Ala Leu Gly Asp Ala Arg Ser Thr Pro Ser Ala Leu Gly Ala Ser 180 185 190

Ser Gly Ile Lys His Glu Arg Ser Met Lys Lys Ala Leu Ala Val Ser 195 200 205

Leu Pro Met Ala Ile Trp Val Phe Ser Cys Ile Thr Thr Ser Leu Ile 210 215 220

Val Met Ser Ala Arg Ile Asp Ser Thr Phe Gly Asn Ala Ile Leu Leu 225 230 235 240

Pro Gly Ile Gly Ala Ala Ile Ala Phe Ser Ala Gly Leu Ile Ala Gln 245 250 255

Phe Leu Gly Arg Lys Phe Ala Trp Gly Arg Gly Ser Gly Ile Val Gly

270

Ala Leu Cys Ala Leu Ala Gly Phe Ala Leu Ala Ala Phe Gly Gly Asp 275 280 285

Ser Ile Pro Val Trp Leu Phe Val Ile Ala Ser Ile Leu Phe Gly Thr 290 295 300

Ala Tyr Gly Leu Cys Leu Arg Glu Gly Leu Leu Ser Ile Glu Thr Tyr 305 310 315 320

Thr Pro Leu Asn Arg Arg Gly Thr Gly Ile Gly Ile Tyr Tyr Val Phe 325 330 335

Thr Tyr Leu Gly Phe Gly Leu Pro Val Leu Leu Asp Ala Leu Leu Pro 340 345 350

His Leu Gly Ala Ser Ile Pro Leu Tyr Ala Leu Ala Ala Leu Ala Leu 355 360 365

Gly Ser Ala Val Ile Arg Gly Val Gln Ile Lys Arg Gly Tyr Val Val 370 375 380

<210> 163

<211> 1130

<212> DNA

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<220>

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<222> (1)..(1107)

<223> FRXA01922

<400> 163

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gtg ttg atc cgt gaa caa tta gac gta tca agc gtg ctg gtc aac ggc 96
Val Leu Ile Arg Glu Gln Leu Asp Val Ser Ser Val Leu Val Asn Gly
20 25 30

gct ttt ggt att tat gca ctg gga ctt ctt cca agt ttg ctc gca ggc 144
Ala Phe Gly Ile Tyr Ala Leu Gly Leu Leu Pro Ser Leu Leu Ala Gly
35 40 45

ggt gtg ctt gcc gac cgt ttt ggt gcc cgc atg gtg gta ctc acc gga 192 Gly Val Leu Ala Asp Arg Phe Gly Ala Arg Met Val Val Leu Thr Gly 50 55 60

ggt gta ctt tct gcg ctt gga aac ctt tct ctt tta gcg ttt cat gat 240
Gly Val Leu Ser Ala Leu Gly Asn Leu Ser Leu Leu Ala Phe His Asp
65 70 75 80

aat	cct	tcc	ctc	ctg	gta	gga	cga	ttc	atc	gtt	ggt	ctg	ggc	gtt	gga	288
ĞÎy	Pro	Ser	Leu	Leu 85	Val	Gly	Arg	Phe	Ile 90	Val	Gly	Leu	Gly	Val 95	Gly	
tta Leu	gtc Val	gtc Val	agc Ser 100	gcg Ala	ggc Gly	acc Thr	gca Ala	tgg Trp 105	gcg. Ala	ggc Gly	aga Arg	ttg Leu	cgc Arg 110	gga Gly	gca Ala	336
agc Ser	ggc Gly	gtg Val 115	aca Thr	ttg Leu	gcc Ala	ggc Gly	att Ile 120	att Ile	ctg Leu	acc Thr	gcc Ala	ggt Gly 125	ttc Phe	atg Met	atg Met	384
ggg Gly	ccg Pro 130	att Ile	gtg Val	aca Thr	agt Ser	ggg Gly 135	ttg Leu	ggg Gly	atg Met	gcg Ala	tcg Ser 140	aca Thr	agc Ser	att Ile	att Ile	432
acg Thr 145	ccc Pro	ttt Phe	gcc Ala	ata Ile	agc Ser 150	gtt Val	gcc Ala	ctc Leu	tcg Ser	ctg Leu 155	atc Ile	gcg Ala	gtg Val	gtt Val	gtg Val 160	480
gga Gly	ttt Phe	gcg Ala	ctt Leu	ggc Gly 165	gat Asp	gcc Ala	cgc Arg	agc Ser	acc Thr 170	ccg Pro	agc Ser	gca Ala	ctt Leu	ggc Gly 175	gca Ala	528
tcc Ser	agc Ser	gga Gly	atc Ile 180	aaa Lys	cac His	gaa Glu	cga Arg	agc Ser 185	atg Met	aaa Lys	aag Lys	gcc Ala	ctc Leu 190	gcg Ala	gtg Val	576
tcc Ser	ttg Leu	ccg Pro 195	atg Met	gca Ala	att Ile	tgg Trp	gtg Val 200	ttc Phe	agc Ser	tgc Cys	atc Ile	acc Thr 205	acc Thr	tcc Ser	ctg Leu	624
atc Ile	gtg Val 210	atg Met	tcc Ser	gcg Ala	cgc Arg	atc Ile 215	gac Asp	tcc Ser	acc Thr	ttc Phe	ggc Gly 220	aac Asn	gcc Ala	att Ile	ctt Leu	672
ctc Leu 225	ccc Pro	gga Gly	atc Ile	ggc Gly	gcg Ala 230	gcg Ala	atc Ile	gcc Ala	ttc Phe	agc Ser 235	gca Ala	ggc Gly	ctg Leu	atc Ile	gca Ala 240	720
caa Gln	ttt Phe	tta Leu	ggt Gly	agg Arg 245	aaa Lys	ttc Phe	gcg Ala	tgg Trp	ggt Gly 250	cgt Arg	ggc Gly	tcc Ser	gga Gly	atc Ile 255	gtg Val	768
ggc Gly	gcg Ala	ctg Leu	tgt Cys 260	gcc Ala	ctc Leu	gcg Ala	ggt Gly	ttt Phe 265	gcg Ala	ctg Leu	gca Ala	gct Ala	ttt Phe 270	ggt Gly	ggc Gly	816
gac Asp	tcc Ser	att Ile 275	cca Pro	gtg Val	tgg Trp	ctt Leu	ttc Phe 280	gtt Val	atc Ile	gcc Ala	tcg Ser	atc Ile 285	ctg Leu	ttc Phe	ggc Gly	864
acc Thr	gca Ala 290	tat Tyr	ggc Gly	ctc Leu	tgc Cys	ctg Leu 295	cgc Arg	gaa Glu	ggc Gly	ctc Leu	ctc Leu 300	agc Ser	atc Ile	gaa Glu	act Thr	912

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	•	0 01	,0000	•												
tac Tyr 305	Thr	cca Pro	cto Lev	c aad 1 Asr	c cga Arg 310	Arg	ggc Gly	acc Thr	ggc	ato Ile 315	Gly	atc Ile	tat Tyr	tat Tyr	gtg Val 320	960
ttc Phe	acg Thr	tat Tyr	ttg Lev	g gga 1 Gly 325	, Phe	ggg Gly	ctg Leu	r cca Pro	gtg Val 330	Leu	cto Leu	gao Asp	gcc Ala	ctc Leu 335	ctc Leu	1008
ccg Pro	cac His	ctt	ggc Gly 340	/ Ala	tco Ser	att Ile	ccg Pro	ctg Leu 345	Tyr	gcg Ala	ctg Leu	gcg Ala	gcg Ala 350	Leu	gcc	1056
ctt Leu	ggc Gly	tcc Ser 355	Ala	gta Val	ato	cgc Arg	ggc Gly 360	Val	caa Gln	atc	aag Lys	cgc Arg 365	Gly	tat Tyr	gtg Val	1104
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Val	Leu	Ile	Arg 20		Gln	Leu	Asp	Val 25	Ser	Ser	Val	Leu	Val 30	Asn	Gly	
Ala	Phe	Gly 35	Ile	Tyr	Ala	Leu	Gly 40	Leu	Leu	Pro	Ser	Leu 45	Leu	Ala	Gly	
Gly	Val 50	Leu	Ala	Asp	Arg	Phe 55	Gly	Ala	Arg	Met	Val 60	Val	Leu	Thr	Gly	
Gly 65	Val	Leu	Ser	Ala	Leu 70	Gly	Asn	Leu	Ser	Leu 75	Leu	Ala	Phe	His	Asp 80	
Gly	Pro	Ser	Leu	Leu 85	Val	Gly	Arg	Phe	Ile 90	Val	Gly	Leu	Gly	Val 95	Gly	•
Leu	Val	Val	Ser 100	Ala	Gly	Thr	Ala	Trp 105	Ala	Gly	Arg	Leu	Arg 110	Gly	Ala	
Ser	Gly	Val 115	Thr	Leu	Ala	Gly	Ile 120	Ile	Leu	Thr	Ala	Gly 125	Phe	Met	Met	
Gly	Pro 130	Ile	Val	Thr	Ser	Gly 135	Leu	Gly	Met	Ala	Ser 140	Thr	Ser	Ile	Ile	
Thr 145	Pro	Phe	Ala	Ile	Ser 150	Val	Ala	Leu	Ser	Leu 155	Ile	Ala	Val	Val	Val 160	

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Gly Phe Ala Leu Gly Asp Ala Arg Ser Thr Pro Ser Ala Leu Gly Ala 165 170 175

Ser Ser Gly Ile Lys His Glu Arg Ser Met Lys Lys Ala Leu Ala Val 180 185 190

Ser Leu Pro Met Ala Ile Trp Val Phe Ser Cys Ile Thr Thr Ser Leu 195 200 205

Ile Val Met Ser Ala Arg Ile Asp Ser Thr Phe Gly Asn Ala Ile Leu 210 215 220

Leu Pro Gly Ile Gly Ala Ala Ile Ala Phe Ser Ala Gly Leu Ile Ala 225 230 235 240

Gln Phe Leu Gly Arg Lys Phe Ala Trp Gly Arg Gly Ser Gly Ile Val 245 250 255

Gly Ala Leu Cys Ala Leu Ala Gly Phe Ala Leu Ala Ala Phe Gly Gly 260 265 270

Asp Ser Ile Pro Val Trp Leu Phe Val Ile Ala Ser Ile Leu Phe Gly 275 280 285

Thr Ala Tyr Gly Leu Cys Leu Arg Glu Gly Leu Leu Ser Ile Glu Thr 290 295 300

Tyr Thr Pro Leu Asn Arg Arg Gly Thr Gly Ile Gly Ile Tyr Tyr Val 305 310 315 320

Phe Thr Tyr Leu Gly Phe Gly Leu Pro Val Leu Leu Asp Ala Leu Leu 325 330 335

Pro His Leu Gly Ala Ser Ile Pro Leu Tyr Ala Leu Ala Ala Leu Ala 340 345 350

Leu Gly Ser Ala Val Ile Arg Gly Val Gln Ile Lys Arg Gly Tyr Val 355 360 365

Val

<210> 165

<211> 362

<212> DNA

<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (1)..(339)

<223> RXA02060

<400> 165

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-		_	-				_		_	_	-	gca Ala		144
												atg Met		192
												tct Ser		240
												cta Leu 95		288
-		Met	_			-		-	_		 _	gaa Glu	_	336
atc Ile	taac	tctt	at c	tcac	tggg	c ct	t							362

<210> 166

<211> 113

<212> PRT

<213> Corynebacterium glutamicum

<400> 166

Glu Phe Ala Arg Ile Leu Lys Pro Lys Gly Gln Val Ile Val Leu Thr 1 5 10 15

Ala Asp Thr Gly His Leu Ala Glu Leu Arg Glu Pro Leu Gly Ile Île 20 25 30

Asp Val Glu Ala Gly Lys Val Asp Arg Met Ile Glu Gln Ala Ala Gly 35 40 45

His Leu Lys Pro Val Gly Glu Arg Asp Leu Val Glu Phe Glu Met Leu 50 55 60

Leu Asp Gln Lys Ser Ile Ala Ser Gln Ile Gly Met Ser Pro Ser Ala 65 70 75 80

Arg His Ile Lys Pro Glu Ala Leu Ala Glu Arg Ile Ala Ala Leu Pro 85 90 95

Glu Gln Met Lys Val Thr Ala Arg Ala Lys Ile Thr Arg Leu Glu Arg 100 105 110

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cta	acaa	ata	ggcc	caac	aa a	agago	ıtcta	ia go	tcta	icctg		Ser			gat Asp 5	115
					Arg					ccg Pro					Leu	163
				Val					Gly	gcc Ala						211
			Val					Met		Gly			Gly			259
										ttg Leu						307
										aaa Lys 80						355
										gcc Ala						403
										ctg Leu						451
										ccc Pro						499
										gcg Ala						547

gtt tat tgg tgc atc atc gcc tgg ggc gca gcc gtt gct ttg ggt ggt Val Tyr Trp Cys Ile Ile Ala Trp Gly Ala Ala Val Ala Leu Gly Gly 295 gtg gca att gtt gtc agc ccc ggc gcg gtg act gcg tgg gcg tgg atg Val Ala Ile Val Val Ser Pro Gly Ala Val Thr Ala Trp Ala Trp Met 315 320 ttc atc atg atg gtc att ggt ggc atg gct gac atg ttc agc tcg Phe Ile Ile Met Met Val Ile Gly Gly Met Ala Asp Met Phe Ser Ser 335 gca gtt cga aac gct att ttg cag cag tct gct gcg gaa cat gtg cag 1171 Ala Val Arg Asn Ala Ile Leu Gln Gln Ser Ala Ala Glu His Val Gln 350 ggc cga atc caa ggt gtg tgg atc atc gtc gtg ggt gga cct cgt 1219 Gly Arg Ile Gln Gly Val Trp Ile Ile Val Val Gly Gly Pro Arg 1267 tta get gae gte ett eac ggt tgg gee get gag eec ete gge gea ggt

1027 1075 1123 WO 01/00804 PCT/IB00/00922

Leu Ala Asp Val Leu His Gry Trp Ala Ala Glu Pro Leu Gly Ala Gly 375 380 385

tgg acg gta tta tgg ggc gga gta gcg gtg gtt gta ctc act gca att 1315 Trp Thr Val Leu Trp Gly Gly Val Ala Val Val Leu Thr Ala Ile 390 395 400 405

tgt atg gtg gcg gtg cct aaa ttc tgg aaa tac gag aaa cca aaa att 1363 Cys Met Val Ala Val Pro Lys Phe Trp Lys Tyr Glu Lys Pro Lys Ile 410 415 420

acc ggc atc taaatactta tccatgccca ttt 1395
Thr Gly Ile

<210> 168

<211> 424

<212> PRT

<213> Corynebacterium glutamicum

<400> 168

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Gln Leu Thr Val Val Ala Val Pro Val Gln Ile Tyr Gln Met Thr Gly 35 40 45

Ser Ser Gly Tyr Val Gly Leu Thr Gly Leu Phe Gly Leu Ile Pro Leu 50 55 60

Val Ile Phe Gly Leu Tyr Gly Gly Ser Ile Ala Asp Ala Phe Asp Lys 65 70 75 80

Arg Ile Val Leu Ile Cys Thr Thr Ile Gly Met Cys Val Thr Thr Ala 85 90 95

Gly Phe Trp Val Leu Thr Ile Leu Gly Asn Glu Asn Ile Trp Leu Leu 100 105 110

Leu Ile Asn Phe Ser Leu Gln Gln Ala Phe Phe Ala Val Asn Gln Pro 115 120 125

Thr Arg Thr Ala Ile Leu Arg Ser Ile Leu Pro Ile Asp Gln Leu Ala 130 135 140

Ser Ala Thr Ser Leu Asn Met Leu Leu Met Gln Thr Gly Ala Ile Val 145 150 155 160

Gly Pro Leu Ile Ala Gly Ala Leu Ile Pro Leu Ile Gly Phe Gly Trp 165 170 175

Leu Tyr Phe Leu Asp Val Val Ser Ile Ile Pro Thr Leu Trp Ala Val 180 185 190 Trp Ser Leu Pro Ser Ile Lys Pro Ser Gly Lys Val Met Lys Ala Gly
195 200 205

Phe Ala Ser Val Val Asp Gly Leu Lys Tyr Leu Ala Gly Gln Pro Val 210 215 220

Leu Leu Met Val Met Val Leu Asp Leu Ile Ala Met Ile Phe Gly Met 225 230 235 240

Pro Arg Ala Leu Tyr Pro Glu Ile Ala Glu Val Asn Phe Gly Gly Gly 245 250 255

Asp Ala Gly Ala Thr Met Leu Ala Phe Met Tyr Ser Ser Met Ala Val 260 265 270

Gly Ala Val Leu Gly Gly Val Leu Ser Gly Trp Val Ala Arg Ile Ser 275 280 285

Arg Gln Gly Val Ala Val Tyr Trp Cys Ile Ile Ala Trp Gly Ala Ala 290 295 300

Val Ala Leu Gly Gly Val Ala Ile Val Val Ser Pro Gly Ala Val Thr 305 310 315 320

Ala Trp Ala Trp Met Phe Ile Ile Met Met Val Ile Gly Gly Met Ala 325 330 335

Asp Met Phe Ser Ser Ala Val Arg Asn Ala Ile Leu Gln Gln Ser Ala 340 345 350

Ala Glu His Val Gln Gly Arg Ile Gln Gly Val Trp Ile Ile Val Val 355 360 365

Val Gly Gly Pro Arg Leu Ala Asp Val Leu His Gly Trp Ala Ala Glu 370 375 380

Pro Leu Gly Ala Gly Trp Thr Val Leu Trp Gly Gly Val Ala Val Val 385 390 395 400

Val Leu Thr Ala Ile Cys Met Val Ala Val Pro Lys Phe Trp Lys Tyr 405 410 415

Glu Lys Pro Lys Ile Thr Gly Ile 420

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<211> 945

<212> DNA

<213> Corynebacterium glutamicum

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205 210 200 tgg atc atc gtc gtg gtg ggt gga cct cgt tta gct gac gtc ctt cac 787 Trp Ile Ile Val Val Val Gly Gly Pro Arg Leu Ala Asp Val Leu His 220 215 ggt tgg gcc gct gag ccc ctc ggc gca ggt tgg acg gta tta tgg ggc 835 Gly Trp Ala Ala Glu Pro Leu Gly Ala Gly Trp Thr Val Leu Trp Gly 235 240 230 gga gta gcg gtg gtt gta ctc act gca att tgt atg gtg gcg gtg cct 883 Gly Val Ala Val Val Leu Thr Ala Ile Cys Met Val Ala Val Pro 260 255 250 aaa ttc tgg aaa tac gag aaa cca aaa att acc ggc atc taaatactta 932 Lys Phe Trp Lys Tyr Glu Lys Pro Lys Ile Thr Gly Ile 945 tccatgccca ttt <210> 170 <211> 274 <212> PRT <213> Corynebacterium glutamicum <400> 170 Met Leu Leu Met Gln Thr Gly Ala Ile Val Gly Pro Leu Ile Ala Gly Ala Leu Ile Pro Leu Ile Gly Phe Gly Trp Leu Tyr Phe Leu Asp Val

Val Ser Ile Ile Pro Thr Leu Trp Ala Val Trp Ser Leu Pro Ser Ile

Lys Pro Ser Gly Lys Val Met Lys Ala Gly Phe Ala Ser Val Val Asp

Gly Leu Lys Tyr Leu Ala Gly Gln Pro Val Leu Leu Met Val Met Val

Leu Asp Leu Ile Ala Met Ile Phe Gly Met Pro Arg Ala Leu Tyr Pro 85

Glu Ile Ala Glu Val Asn Phe Gly Gly Gly Asp Ala Gly Ala Thr Met 105

Leu Ala Phe Met Tyr Ser Ser Met Ala Val Gly Ala Val Leu Gly Gly 115 120

Val Leu Ser Gly Trp Val Ala Arg Ile Ser Arg Gln Gly Val Ala Val

Tyr Trp Cys Ile Ile Ala Trp Gly Ala Ala Val Ala Leu Gly Gly Val 160 145

WO 01/00804 Ala Ile Val. Val Ser Pro Gly Ala Val Thr Ala Trp Ala Trp Met Phe Ile Ile Met Met Val Ile Gly Gly Met Ala Asp Met Phe Ser Ser Ala 185 180 Val Arg Asn Ala Ile Leu Gln Gln Ser Ala Ala Glu His Val Gln Gly 200 Arg Ile Gln Gly Val Trp Ile Ile Val Val Gly Gly Pro Arg Leu Ala Asp Val Leu His Gly Trp Ala Ala Glu Pro Leu Gly Ala Gly Trp Thr Val Leu Trp Gly Gly Val Ala Val Val Leu Thr Ala Ile Cys 245 Met Val Ala Val Pro Lys Phe Trp Lys Tyr Glu Lys Pro Lys Ile Thr 265 Gly Ile <210> 171 <211> 549 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (101)..(526) <223> FRXA01937 <400> 171 gcgcggtgac accacagccg ttgtcagcgg cgcttggtct gtggaggatc gccgaggtta 60 ctaacaaata ggcccaacaa agaggtctaa gctctacctg gtg agt ttc cga qat Val Ser Phe Arg Asp att ttc gct gac acc aga ccg ctg aaa gaa ccg gcc ttc aaa cgc ctc Ile Phe Ala Asp Thr Arg Pro Leu Lys Glu Pro Ala Phe Lys Arg Leu

163 10 211 tgg ctt ggc aat gtt gcc acc gtc att ggt gcc caa tta act gtt gtt Trp Leu Gly Asn Val Ala Thr Val Ile Gly Ala Gln Leu Thr Val Val gcc gtt ccg gtg cag att tac caa atg act ggg tcc tcc ggc tat gtg 259 Ala Val Pro Val Gln Ile Tyr Gln Met Thr Gly Ser Ser Gly Tyr Val 45 ggc ttg acc ggg ctt ttt ggc ctt att cct ttg gtt att ttt ggc ctt 307 Gly Leu Thr Gly Leu Phe Gly Leu Ile Pro Leu Val Ile Phe Gly Leu 60

tat ggt gga tcc att gcg gat gct ttt gat aaa cgc atc gtg ctg at Tyr Gly Gly Ser Ile Ala Asp Ala Phe Asp Lys Arg Ile Val Leu II 70 75 80	.c 355 .e
tgc acc acg atc ggc atg tgt gtc acc act gcc ggt ttt tgg gtg ct Cys Thr Thr Ile Gly Met Cys Val Thr Thr Ala Gly Phe Trp Val Le 90 95 100	.g 403 eu
acc att tta ggc aat gag aat att tgg ctc ctg tta ata aac ttt tc Thr Ile Leu Gly Asn Glu Asn Ile Trp Leu Leu Leu Ile Asn Phe Se 105 110 115	t 451
tta cag cag gca ttt ttc gcg gtg aat caa ccc acc cga acg gcg at Leu Gln Gln Ala Phe Phe Ala Val Asn Gln Pro Thr Arg Thr Ala II 120 125 130	e 499
ctt cga agt att ttg ccg att gat caa taagcgtcgg caacatcact Leu Arg Ser Ile Leu Pro Ile Asp Gln 135 140	546
gaa	549
<210> 172 <211> 142 <212> PRT <213> Corynebacterium glutamicum	
<pre><400> 172 Val Ser Phe Arg Asp Ile Phe Ala Asp Thr Arg Pro Leu Lys Glu Pr 1 5 10 15</pre>	o
Val Ser Phe Arg Asp Ile Phe Ala Asp Thr Arg Pro Leu Lys Glu Pr	
Val Ser Phe Arg Asp Ile Phe Ala Asp Thr Arg Pro Leu Lys Glu Pr 1 5 10 15 Ala Phe Lys Arg Leu Trp Leu Gly Asn Val Ala Thr Val Ile Gly Al	a
Val Ser Phe Arg Asp Ile Phe Ala Asp Thr Arg Pro Leu Lys Glu Pro 1 10 15 Ala Phe Lys Arg Leu Trp Leu Gly Asn Val Ala Thr Val Ile Gly Ala 20 25 30 Gln Leu Thr Val Val Ala Val Pro Val Gln Ile Tyr Gln Met Thr Gl	a y
Val Ser Phe Arg Asp Ile Phe Ala Asp Thr Arg Pro Leu Lys Glu Pro 10 15 Ala Phe Lys Arg Leu Trp Leu Gly Asn Val Ala Thr Val Ile Gly Ala 20 Gln Leu Thr Val Val Ala Val Pro Val Gln Ile Tyr Gln Met Thr Gly 35 Ser Ser Gly Tyr Val Gly Leu Thr Gly Leu Phe Gly Leu Ile Pro Leu 50 Val Ile Phe Gly Leu Tyr Gly Gly Ser Ile Ala Asp Ala Phe Asp Ly	a Y u
Val Ser Phe Arg Asp Ile Phe Ala Asp Thr Arg Pro Leu Lys Glu Pro 10 15 Ala Phe Lys Arg Leu Trp Leu Gly Asn Val Ala Thr Val Ile Gly Ala 20 Gln Leu Thr Val Val Ala Val Pro Val Gln Ile Tyr Gln Met Thr Gly 35 Ser Ser Gly Tyr Val Gly Leu Thr Gly Leu Phe Gly Leu Ile Pro Leu So So So So So So So So So So So So So	a y u s 0
Val Ser Phe Arg Asp Ile Phe Ala Asp Thr Arg Pro Leu Lys Glu Pro 10	a y u s 0
Val Ser Phe Arg Asp Ile Phe Ala Asp Thr Arg Pro Leu Lys Glu Pro 10	a y u s 0 a

<2 <2	10> 11> 12> 13>	1242 DNA		cter	ium	glut	amic	um								
<2 <2		(101)(1010	1219)											
	00> gcca		gtt	tcct	gta a	aaac	gcata	aa c	ccg	aata	c cc	cctgt	ttc	caga	atccaaa	60
aa	aaga	tctg	gca	3 333	gtt 1	tagg	cataç	ga ti	agga	aact	Met	-	-		g caa 1 Gln 5	115
					Val					L Gly					caa Gln	163
				. Val					Ala					Ile	agt Ser	211
			ı Ala					Thr					Pro		gcc Ala	259
		Met					Arg					Ile			cat His	307
	Val					Tyr					Pro				ttg Leu 85	355
					Ser							gcg Ala			acg Thr	403
												caa Gln				451
cgt Arg	gag Glu	ctt Leu 120	gtt Val	ccg Pro	ccg Pro	cgt Arg	tct Ser 125	ttg Leu	ggt Gly	aag Lys	gca Ala	ttg Leu 130	ggc Gly	acc Thr	tat Tyr	499
gct Ala	gcg Ala 135	atg Met	caa Gln	tca Ser	ctc Leu	ggc Gly 140	atg Met	ttg Leu	tcg Ser	gcg Ala	cca Pro 145	ctg Leu	atc Ile	gca Ala	ggt Gly	547
gtg Val 150	tct Ser	tcg Ser	gtg Val	gtg Val	tcg Ser 155	tgg Trp	agg Arg	ttg Leu	acc Thr	ttc Phe 160	ctg Leu	gtc Val	act Thr	gca Ala	gca Ala 165	595

							,									
					Let					Pro					cca Pro	643
				Glr					/ Lys					Pro	acc Thr	691
			Met					. Val					, Ile		ggc Gly	739
		/ Phe					His		ggc Gly			Phe			gat Asp	787
	Ala								tgt Cys		Gly				ttc Phe 245	835
									gca Ala 255							883
									ggt Gly							931
									gtg Val							979
									gca Ala							1027
									ctt Leu							1075
									gtg Val 335							1123
									gtc Val							1171
ttc Phe	gtt Val	gcc Ala 360	atc Ile	gcc Ala	cag Gln	Trp	ctc Leu 365	aac Asn	ccg Pro	cag Gln	cgg Arg	gtg Val 370	gag Glu	cgg Arg	ggc Gly	1219

PCT/IB00/00922

1242

<210> 174

tgagggagac gtcgagaagc gtc

WO 01/00804

<211> 373

<212> PRT

<213> Corynebacterium glutamicum

<400> 174

Met Lys Lys Leu Gln Met Pro Ala Ile Leu Val Gly Gly Phe Val Gly
1 5 10 15

Pro Phe Thr Gly Gln Ala Leu Ser Val Val Leu Pro Glu Phe Ala Asp 20 25 30

Thr Phe Asp Ile Ser Val Ser Gln Ala Ala Leu Thr Met Thr Ala Tyr
35 40 45

Leu Leu Pro Phe Ala Thr Met Met Leu Phe Ser Gly Arg Ile Thr Arg 50 55 60

Lys Ile His Pro His Lys Val Val Gln Ala Ala Tyr Ile Val Thr Leu 65 70 75 80

Pro Leu Ala Leu Leu Leu Val Thr Pro Ser Trp Gly Leu Phe Met 85 90 95

Ala Ala Tyr Ala Thr Ile Gly Ile Ala Asn Ala Phe Thr Thr Pro Val

Leu Gln Ile Met Leu Arg Glu Leu Val Pro Pro Arg Ser Leu Gly Lys 115 120 125

Ala Leu Gly Thr Tyr Ala Ala Met Gln Ser Leu Gly Met Leu Ser Ala 130 135 140

Pro Leu Ile Ala Gly Val Ser Ser Val Val Ser Trp Arg Leu Thr Phe 145 150 155 160

Leu Val Thr Ala Ala Ala Ser Leu Phe Ile Leu Val Ala Arg Leu Pro

Val Val Pro Pro Pro Ser Ala Ser Lys Gln Asn Val Ser Gly Lys Val 180 185 190

Gln Trp Gly Pro Thr Ile Ile His Met Val Ser Gly Phe Val Val Gly
195 200 205

Ile Gly Ile Ile Gly Ile Gly Phe Met Thr Ser Leu His Val Gly Glu 210 215 220

Gln Phe Gly Leu Asp Ala Ala Ala Arg Gly Leu Val Val Met Cys Gly 225 230 235 240

Gly Leu Ala Ala Phe Phe Ala Ser Arg Lys Ile Gly Asp Leu Ala Asp 245 250 255

Lys Phe Gly Val Arg Ala Val Leu Ile Val Ser Ala Val Ile Gly Thr 260 265 270

Ile Ala Leu Ala Leu Leu Pro Ile Ala Pro Trp Ile Ile Val Val Ala

WO 01/00804 280 275 Val Leu Trp Ala Phe Ala Val Ala Ala Ala Gln Gly Ile Gln Ala Thr 295 Val Asn Leu Ala Val Ile Gly Ser Pro Gly Gly Ser Ser Leu Leu Ser Thr Val Gln Ala Phe Arg Phe Phe Gly Ser Ala Ala Ala Pro Val Thr Phe Leu Pro Ile Tyr Met Gly Ile Gly Ser Gly Ala Phe Trp Val Ser Ala Val Ala Leu Phe Phe Val Ala Ile Ala Gln Trp Leu Asn Pro Gln Arg Val Glu Arg Gly 370 <210> 175 <211> 871 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (101)..(871) <223> FRXA01010 <400> 175

gtgccaaagc gtttcctgta aaacgcataa ccccgaatac cccctgtttc cagatccaaa 60

aaaagatetg geagggggtt taggeataga ttaggaactt atg aag aaa etg caa 115 Met Lys Lys Leu Gln

atg ccg gcc att ttg gtc gga ggc ttt gtg ggg ccg ttt act ggc caa 163 Met Pro Ala Ile Leu Val Gly Gly Phe Val Gly Pro Phe Thr Gly Gln

got ota toa gtg gtc ttg cog gaa ttt gca gac acc ttt gat atc agt 211 Ala Leu Ser Val Val Leu Pro Glu Phe Ala Asp Thr Phe Asp Ile Ser

gtc agc cag gca gcg ctg acc atg acc gca tac ttg ttg ccc ttt gcc 259 Val Ser Gln Ala Ala Leu Thr Met Thr Ala Tyr Leu Leu Pro Phe Ala 40

acc atg atg ttg ttt tcg ggg cgc atc acc aga aag atc cat ccg cat 307 Thr Met Met Leu Phe Ser Gly Arg Ile Thr Arg Lys Ile His Pro His

aag gtg gtg cag gcg gct tat att gtc aca ctg cca ctt gcg ctg ttg 355 Lys Val Val Gln Ala Ala Tyr Ile Val Thr Leu Pro Leu Ala Leu Leu 70

			cca Pro	Ser				Met			403
			aat Asn								451
			ccg Pro								499
			tca Ser								547
			gtg Val								595
			att Ile 170								643
			caa Gln								691
			gtt Val								739
			aca Thr								787
			ggt Gly								835
	-	-	aag Lys 250		 -	Leu	-	-			871

<210> 176

<211> 257

<212> PRT

<213> Corynebacterium glutamicum

<400> 176

Met Lys Lys Leu Gln Met Pro Ala Ile Leu Val Gly Gly Phe Val Gly 1 5 10 15

Pro Phe Thr Gly Gln Ala Leu Ser Val Val Leu Pro Glu Phe Ala Asp 20 25 30

Thr Phe Asp Ile Ser Val Ser Gln Ala Ala Leu Thr Met Thr Ala Tyr
35 40 45

Leu Leu Pro Phe Ala Thr Met Met Leu Phe Ser Gly Arg Ile Thr Arg
50 55 60

Lys Ile His Pro His Lys Val Val Gln Ala Ala Tyr Ile Val Thr Leu 65 70 75 80

Pro Leu Ala Leu Leu Leu Val Thr Pro Ser Trp Gly Leu Phe Met 85 90 95

Ala Ala Tyr Ala Thr Ile Gly Ile Ala Asn Ala Phe Thr Thr Pro Val 100 105 110

Leu Gln Ile Met Leu Arg Glu Leu Val Pro Pro Arg Ser Leu Gly Lys 115 120 125

Ala Leu Gly Thr Tyr Ala Ala Met Gln Ser Leu Gly Met Leu Ser Ala 130 135 140

Pro Leu Ile Ala Gly Val Ser Ser Val Val Ser Trp Arg Leu Thr Phe 145 150 155 160

Leu Val Thr Ala Ala Ala Ser Leu Phe Ile Leu Val Ala Arg Leu Pro 165 170 175

Val Val Pro Pro Pro Ser Ala Leu Lys Gln Asn Val Ser Gly Lys Val 180 185 190

Gln Trp Gly Pro Thr Ile Ile His Met Val Ser Gly Phe Val Val Gly
195 200 205

Ile Gly Ile Ile Gly Ile Gly Phe Met Thr Ser Leu His Val Gly Glu 210 215 220

Gln Phe Gly Leu Asn Thr Ala Ala Arg Gly Leu Val Val Met Cys Gly 225 230 235 240

Gly Arg Ala Ala Phe Phe Ala Ser Arg Lys Ile Gly Asp Leu Ala Asp 245 250 255

Lys

<210> 177

<211> 1266

<212> DNA

<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (101)..(1243)

<223> RXN03142

WO 01/00804 PCT/IB00/00922

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200 205 210

		Ala				Ile				aac Asn 225				caa Gln	787
	Thr									ttt Phe					835
				Met						cgc Arg					883
										atc Ile					931
										tgg Trp					979
										atc Ile 305					1027
										cag Gln					1075
										att Ile					1123
										tac Tyr					1171
					Ile					gtg Val					1219
_	_			Ala	-		taag	ttag	ag c	attt	tatt	g ag	c		1266

<210> 178

<211> 381

<212> PRT

<213> Corynebacterium glutamicum

<400> 178

Val Phe Ile Leu Gly Trp Leu Val Asn Leu Thr Gln Tyr Leu Ser Phe 1 5 10 15

Tyr Phe Leu Ile Thr Val Met Ala Leu Tyr Ala Met Glu Ser Phe Ala

Val Ser Glu Ala Ala Val Gly Phe Ala Ala Ser Ser Phe Val Ile Gly 35 40 45

Ala Thr Val Ala Arg Val Phe Ala Gly Trp Thr Ser Asp Arg Phe Gly 50 55 60

Lys Lys Gln Ile Leu Leu Ile Phe Val Gly Leu Glu Ala Val Ala Ser
65 70 75 80

Leu Phe Tyr Ile Pro Ala Ala Ser Leu Pro Ala Leu Val Ala Val Arg 85 90 95

Phe Val His Gly Phe Ser Tyr Ser Leu Ala Ser Thr Ala Val Met Ala 100 105 110

Leu Val Gln Ser Val Ile Pro Ala Ser Arg Arg Ala Glu Gly Thr Gly
115 120 125

Tyr Phe Ala Leu Gly Ser Thr Leu Ala Thr Ala Phe Gly Pro Ala Ile 130 135 140

Ala Leu Phe Val Ile Asp Asp Phe Asn Tyr Asn Thr Leu Phe Trp Ile 145 150 155 160

Thr Thr Ala Thr Ser Val Phe Gly Leu Ile Leu Thr Val Leu Ile Arg 165 170 175

Lys Pro Glu Phe Ile Lys Asn Ala Glu His Gly Arg Val Lys Pro Val 180 185 190

Trp Ser Ile Lys Thr Val Val His Pro Ser Val Met Leu Ile Gly Phe 195 200 205

Phe Met Leu Ala Val Gly Leu Ala Tyr Ala Gly Val Ile Thr Phe Leu 210 215 220

Asn Gly Phe Ala Gln Asp Thr Gly Leu Thr Ala Gly Ala Gly Leu Phe 225 230 235 240

Phe Ile Ala Tyr Ala Val Ala Met Leu Val Met Arg Phe Phe Leu Gly 245 250 255

Arg Ile Gln Asp Lys His Gly Asp Asn Pro Val Ile Tyr Phe Gly Leu 260 265 270

Ile Ser Phe Ala Leu Ala Leu Gly Leu Met Ala Leu Ala Thr Glu Asp 275 280 285

Trp His Ile Val Leu Ala Gly Ala Leu Thr Gly Leu Gly Tyr Gly Thr 290 295 300

Ile Met Pro Ala Ala Gln Ala Ile Ala Val Asp Ser Val Pro Ser Thr 305 310 315 320

Gln Val Gly Ser Gly Ile Ser Thr Leu Phe Leu Phe Thr Asp Ile Gly

Ile Gly Leu Gly Pro Ile Leu Leu Gly Gly Leu Val Ala Ala Thr Gly 340 345 350

Tyr Asn Val Met Tyr Ala Ala Leu Ala Ala Val Ile Val Val Ala Gly
355 360 365

Val Leu Tyr Leu Val Ala Leu Gly Arg Lys Ala Ser His 370 375 380

<210> 179

<211> 914

<212> DNA

<213> Corynebacterium glutamicum

<220>

<221> CDS

<222> (1)..(891)

<223> FRXA01150

<400> 179

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Pro Ala Ala Ser Leu Pro Ala Leu Val Ala Val Arg Phe Val His Gly
1 5 10 15

ttt tct tat tct ctt gct tcc acc gct gtg atg gca ctt gtg cag tcc 96
Phe Ser Tyr Ser Leu Ala Ser Thr Ala Val Met Ala Leu Val Gln Ser
20 25 30

gtg att cct gca agc cgt agg gca gag ggc acc ggc tac ttc gcg ctc 144 Val Ile Pro Ala Ser Arg Arg Ala Glu Gly Thr Gly Tyr Phe Ala Leu 35 40 45

gga tcc aca ctg gct aca gct ttc ggc cca gca att gcg ctg ttt gtt 192 Gly Ser Thr Leu Ala Thr Ala Phe Gly Pro Ala Ile Ala Leu Phe Val 50 55 60

atc gat gac ttc aac tac aac acc ctg ttc tgg att acc act gcg acc

Ile Asp Asp Phe Asn Tyr Asn Thr Leu Phe Trp Ile Thr Thr Ala Thr

65 70 75 80

agt gtt ttc ggc ctg atc ctc acc gtt ttg atc cgc aag ccg gag ttc 288
Ser Val Phe Gly Leu Ile Leu Thr Val Leu Ile Arg Lys Pro Glu Phe
85 90 95

att aag aat gcg gaa cac ggc aga gta aag cca gtc tgg tct atc aag 336 Ile Lys Asn Ala Glu His Gly Arg Val Lys Pro Val Trp Ser Ile Lys 100 105 110

act gtt gtg cac cca tcg gtc atg ctc att gga ttc ttc atg ctc gct 384
Thr Val Val His Pro Ser Val Met Leu Ile Gly Phe Phe Met Leu Ala
115 120 125

gtc gga ctg gct tac gca ggc gtg atc acc ttc ctc aac ggc ttc gcg 432 Val Gly Leu Ala Tyr Ala Gly Val Ile Thr Phe Leu Asn Gly Phe Ala

1 35

140

	Asp								Phe			gct Ala		480
				Val				Leu				cag Gln 175		528
		 -	Asn	_	_				_		_	ttc Phe	-	576
												att Ile		624
												ccg Pro		672
												ggt Gly		720
												tta Leu 255		768
												gtc Val		816
												tac Tyr		864
				aaa Lys			taag	rttag	ag c	attt	tatt	ģ		911
agc														914

<210> 180

<211> 297

<212> PRT

<213> Corynebacterium glutamicum

<400> 180

Pro Ala Ala Ser Leu Pro Ala Leu Val Ala Val Arg Phe Val His Gly
1 5 10 15

Phe Ser Tyr Ser Leu Ala Ser Thr Ala Val Met Ala Leu Val Gln Ser 20 25 30

Val Ile Pro Ala Ser Arg Arg Ala Glu Gly Thr Gly Tyr Phe Ala Leu 35 40 45

Gly Ser Thr Leu Ala Thr Ala Phe Gly Pro Ala Ile Ala Leu Phe Val 50 55 60

Ile Asp Asp Phe Asn Tyr Asn Thr Leu Phe Trp Ile Thr Thr Ala Thr 65 70 75 80

Ser Val Phe Gly Leu Ile Leu Thr Val Leu Ile Arg Lys Pro Glu Phe 85 90 95

Ile Lys Asn Ala Glu His Gly Arg Val Lys Pro Val Trp Ser Ile Lys
100 105 110

Thr Val Val His Pro Ser Val Met Leu Ile Gly Phe Phe Met Leu Ala 115 120 125

Val Gly Leu Ala Tyr Ala Gly Val Ile Thr Phe Leu Asn Gly Phe Ala 130 135 140

Gln Asp Thr Gly Leu Thr Ala Gly Ala Gly Leu Phe Phe Ile Ala Tyr 145 150 155 160

Ala Val Ala Met Leu Val Met Arg Phe Phe Leu Gly Arg Ile Gln Asp 165 170 175

Lys His Gly Asp Asn Pro Val Ile Tyr Phe Gly Leu Ile Ser Phe Ala 180 185 190

Leu Ala Leu Gly Leu Met Ala Leu Ala Thr Glu Asp Trp His Ile Val 195 200 205

Leu Ala Gly Ala Leu Thr Gly Leu Gly Tyr Gly Thr Ile Met Pro Ala 210 215 220

Ala Gln Ala Ile Ala Val Asp Ser Val Pro Ser Thr Gln Val Gly Ser 225 230 235 240

Gly Ile Ser Thr Leu Phe Leu Phe Thr Asp Ile Gly Ile Gly Leu Gly 245 250 255

Pro Ile Leu Gly Gly Leu Val Ala Ala Thr Gly Tyr Asn Val Met 260 265 270

Tyr Ala Ala Leu Ala Ala Val Ile Val Val Ala Gly Val Leu Tyr Leu 275 280 285

Val Ala Leu Gly Arg Lys Ala Ser His 290 295

<210> 181

<211> 1341

<212> DNA

<213> Corynebacterium glutamicum

<220> <221> CDS <222> (101)..(1318) <223> RXN02964

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												a gte Val	g tc	c gta	a gct	gaa Glu 5	115
	gaa Glu	a gg	g aa y Ly	a ct s Le	t tt u Ph	e Th	a cc r Pr	a aco	g tti	t gte e Val	l Met	g gga t Gly	a tgo / Trp	ttt Phe	gco Ala 20	aac Asn	163
					e Le				c tto r Phe 30	e Let					Ala	ttg Leu	211
	tac Tyr	gco Ala	a Ile	e Lys	g gaa s Glu	a ttt 1 Phe	t caa e Glr	a geo n Ala 45	a Ser	gaa Glu	a gta 1 Val	a gaa L Glu	gct Ala 50	Gly	ttc Phe	gca Ala	259
	tcc Ser	ago Ser 55	: Sei	a att	gtt Val	ato Ile	ggc Gly 60	/ Ala	gtc Val	ttt Phe	tcc Ser	agg Arg 65	Phe	ttc Phe	tcc Ser	ggc	307
	tat Tyr 70	Ile	att Ile	gac Asp	cgt Arg	ttt Phe 75	Gly	cga Arg	cgc Arg	aag Lys	att Ile 80	Val	ctc Leu	atc Ile	tca Ser	gtc Val 85	355
	cta Leu	gto Val	act Thr	acc Thr	att Ile 90	Ala	tgt Cys	gcc Ala	ttg Leu	tac Tyr 95	ctt Leu	ccc Pro	atc Ile	gaa Glu	tca Ser 100	ttg Leu	403
	cca Pro	ttg Leu	cta Leu	tac Tyr 105	Ala	aac Asn	agg Arg	ttc Phe	ctc Leu 110	cac His	ggt Gly	gtt Val	gga Gly	tac Tyr 115	gct Ala	ttt Phe	451
	gct Ala	gcc Ala	acc Thr 120	gcg Ala	atc Ile	atg Met	gca Ala	atg Met 125	gtc Val	cag Gln	gag Glu	ctc Leu	att Ile 130	cca Pro	gcg Ala	tca Ser	499
	cga Arg	cgt Arg 135	tcc Ser	gaa Glu	ggt Gly	act Thr	ggt Gly 140	tac Tyr	ctg Leu	gca Ala	ttg Leu	ggc Gly 145	act Thr	acc Thr	gtt Val	tct Ser	547
	gca Ala 150	gca Ala	ctt Leu	gga Gly	cca Pro	gcc Ala 155	cta Leu	gca Ala	ctt Leu	ttt Phe	gtc Val 160	cta Leu	gga Gly	aca Thr	ttt Phe	gat Asp 165	595
,	tac Tyr	gac Asp	atg Met	Leu	ttt Phe 170	atc Ile	gtg Val	gtc Val	ttg Leu	gca Ala 175	acc Thr	tcg Ser	gtc Val	atc Ile	tct Ser 180	ttg Leu	643
ć	atc	gcc	gtc	gtg	ttc	atg	tac	ttt	aag	acc	agc	gac	cct	gag	cct	tct	691

Ser

<210> 182 <211> 406 <212> PRT <213> Corynebacterium glutamicum <400> 182 Val Ser Val Ala Glu Glu Gly Lys Leu Phe Thr Pro Thr Phe Val Met Gly Trp Phe Ala Asn Leu Phe Gln Phe Leu Val Phe Tyr Phe Leu Ile Thr Thr Met Ala Leu Tyr Ala Ile Lys Glu Phe Gln Ala Ser Glu Val Glu Ala Gly Phe Ala Ser Ser Ser Ile Val Ile Gly Ala Val Phe Ser Arg Phe Phe Ser Gly Tyr Ile Ile Asp Arg Phe Gly Arg Arg Lys Ile 65 Val Leu Ile Ser Val Leu Val Thr Thr Ile Ala Cys Ala Leu Tyr Leu Pro Ile Glu Ser Leu Pro Leu Leu Tyr Ala Asn Arg Phe Leu His Gly 100 105 Val Gly Tyr Ala Phe Ala Ala Thr Ala Ile Met Ala Met Val Gln Glu 120 Leu Ile Pro Ala Ser Arg Arg Ser Glu Gly Thr Gly Tyr Leu Ala Leu 130 135 Gly Thr Thr Val Ser Ala Ala Leu Gly Pro Ala Leu Ala Leu Phe Val Leu Gly Thr Phe Asp Tyr Asp Met Leu Phe Ile Val Val Leu Ala Thr Ser Val Ile Ser Leu Ile Ala Val Val Phe Met Tyr Phe Lys Thr Ser Asp Pro Glu Pro Ser Gly Glu Pro Ala Lys Phe Ser Phe Lys Ser Ile 195 Met Asn Pro Lys Ile Ile Pro Ile Gly Ile Phe Ile Leu Leu Ile Cys

Phe Ala Tyr Ser Gly Val Ile Ala Tyr Ile Asn Ala Phe Ala Glu Glu

Arg Asp Leu Ile Thr Gly Ala Gly Leu Phe Phe Ile Ala Tyr Ala Val

230

250

Ser	Met	Phe	Val 260		Arg	Ser	Phe	Leu 265		Lys	Leu	Gln	Asp 270	_	Arg	
Gly	Asp	Asn 275		Val	Ile	Tyr	Phe 280	_	Leu	Phe	Phe	Phe 285	Val	. Ile	Ser	
Leu	Thr 290		Leu	Ser	Phe	Ala 295		Ser	Asn	Trp	His 300		Val	Leu	ser	
Gly 305		Ile	Ala	Gly	Leu 310	Gly	Tyr	Gly	Thr	Leu 315	Met	Pro	Ala	Val	. Gln 320	
Ser	Ile	Ala	Val	Gly 325	Val	Val	Asp	Lys	Thr 330	Glu	Phe	Gly	Thr	Ala 335	Phe	
Ser	Thr	Leu	Phe 340	Leu	Phe	Val	Asp	Leu 345	Gly	Phe	Gly	Phe	Gly 350		Ile	
Ile	Leu	Gly 355	Ala	Val	Ser	Ala	Ala 360	Ile	Gly	Phe	Gly	Pro 365	Met	Туг	Ala	
Ala	Leu 370	Ala	Gly	Val	Gly	Val 375	Ile	Ala	Gly	Ile	Phe 380	Tyr	Leu	Phe	Thr	
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Pro	Val	Ala	Leu	Val 405	Ser											
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<220 <221)> .> CD	s														
	!> (1 !> FR			06)									•		v.	
	> 18 atat		agcaa	agggt	t gti	tgca	tgat	gca	ataa	acg	tggt	agtt	tg t	gtto	cataac	60
aaaa	ttgc	at ga	atgca	aataa	a tti	toga	ttta	aag	gaga			tcc Ser	-	-	_	115
	ggg a Gly 1															163
	ttc (Phe (211
tac (gcc a	atc a	ag g	aa t	tt c	aa g	jcc t	ct g	jaa g	ıta ç	gaa q	gct g	gc ·	ttc	gca	259

Tyr Ala Ile Lys Glu Phe Gin Ala Ser Glu Val Glu Ala Gly Phe Ala 45 tcc agc tca att gtt atc ggc gca gtc ttt tcc agg ttt ttc tcc ggc Ser Ser Ser Ile Val Ile Gly Ala Val Phe Ser Arg Phe Phe Ser Gly 60 tat att att gac cgt ttt ggt cga cgc aag att gtg ctc atc tca gtc 355 Tyr Ile Ile Asp Arg Phe Gly Arg Arg Lys Ile Val Leu Ile Ser Val cta gtc act acc att gcg tgt gcc ttg tac ctt ccc atc gaa tca ttg 403 Leu Val Thr Thr Ile Ala Cys Ala Leu Tyr Leu Pro Ile Glu Ser Leu cca ttg cta tac gca aac agg ttc ctc cac ggt gtt gga tac gct ttt 451 Pro Leu Leu Tyr Ala Asn Arg Phe Leu His Gly Val Gly Tyr Ala Phe get gee ace geg ate atg gea atg gte eag gag ete att eea geg tea 499 Ala Ala Thr Ala Ile Met Ala Met Val Gln Glu Leu Ile Pro Ala Ser cga cgt tcc gaa ggt act ggt tac ctg gca ttg ggc act acc gtt tct 547 Arg Arg Ser Glu Gly Thr Gly Tyr Leu Ala Leu Gly Thr Thr Val Ser gca gca ctt gga cca gcc cta gca ctt ttt gtc cta gga aca ttt gat 595 Ala Ala Leu Gly Pro Ala Leu Ala Leu Phe Val Leu Gly Thr Phe Asp 160 tac gac atg ctg ttt atc gtg gtc ttg gca acc tcg gtc atc tct ttg 643 Tyr Asp Met Leu Phe Ile Val Val Leu Ala Thr Ser Val Ile Ser Leu atc gcc gtc gtg ttc atg tac ttt aag acc agc gac cct gag cct tct 691 Ile Ala Val Val Phe Met Tyr Phe Lys Thr Ser Asp Pro Glu Pro Ser 185 190 ggg gaa cca gcc aag ttc agc ttc aaa tct att atq aac cca aaq atc 739 Gly Glu Pro Ala Lys Phe Ser Phe Lys Ser Ile Met Asn Pro Lys Ile 200 ate eee ate gge ate ttt ate ttg ett att tge ttt get tae tet gge 787 Ile Pro Ile Gly Ile Phe Ile Leu Leu Ile Cys Phe Ala Tyr Ser Gly gtc att gcc tac atc aac gca ttt gct gaa gaa cgc gat ctg att acg 835 Val Ile Ala Tyr Ile Asn Ala Phe Ala Glu Glu Arg Asp Leu Ile Thr 230 240 ggt gct gga ttg ttc ttc att gcc tac gca gta tca atg ttt gtg atg 883 Gly Ala Gly Leu Phe Phe Ile Ala Tyr Ala Val Ser Met Phe Val Met 250 cgc agc ttc ctt ggc aaa ctg cag gac cgt cgc gga gac aac gtc gtt 931 Arg Ser Phe Leu Gly Lys Leu Gln Asp Arg Arg Gly Asp Asn Val Val

275

att tac ttt gga ttg ttc ttc ttc gtt att tcc ttg acg att ttg tcc

Ile Tyr Phe Gly Leu Phe Phe Phe Val Ile Ser Leu Thr Ile Leu Ser

280 285 290

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<211> 302

<212> PRT

<213> Corynebacterium glutamicum

<400> 184

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Thr Thr Met Ala Leu Tyr Ala Ile Lys Glu Phe Gln Ala Ser Glu Val 35 40 45

Glu Ala Gly Phe Ala Ser Ser Ser Ile Val Ile Gly Ala Val Phe Ser 50 55 60

Arg Phe Phe Ser Gly Tyr Ile Ile Asp Arg Phe Gly Arg Arg Lys Ile
65 70 75 80

Val Leu Ile Ser Val Leu Val Thr Thr Ile Ala Cys Ala Leu Tyr Leu 85 90 95

Pro Ile Glu Ser Leu Pro Leu Leu Tyr Ala Asn Arg Phe Leu His Gly
100 105 110

Val Gly Tyr Ala Phe Ala Ala Thr Ala Ile Met Ala Met Val Gln Glu 115 120 125

Leu Ile Pro Ala Ser Arg Arg Ser Glu Gly Thr Gly Tyr Leu Ala Leu 130 135 140

Gly Thr Thr Val Ser Ala Ala Leu Gly Pro Ala Leu Ala Leu Phe Val 145 150 155 160

Leu Gly Thr Phe Asp Tyr Asp Met Leu Phe Ile Val Val Leu Ala Thr 165 170 175

Ser Val Ile Ser Leu Ile Ala Val Val Phe Met Tyr Phe Lys Thr Ser 180 185 190

Asp Pro Glu Pro Ser Gly Glu Pro Ala Lys Phe Ser Phe Lys Ser Ile 195 200 205

Met Asn Pro Lys Ile Ile Pro Ile Gly Ile Phe Ile Leu Leu Ile Cys

210 215 220

Phe Ala Tyr Ser Gly Val Ile Ala Tyr Ile Asn Ala Phe Ala Glu Glu 225 235 240

Arg Asp Leu Ile Thr Gly Ala Gly Leu Phe Phe Ile Ala Tyr Ala Val 245 250 255

Ser Met Phe Val Met Arg Ser Phe Leu Gly Lys Leu Gln Asp Arg Arg 260 265 270

Gly Asp Asn Val Val Ile Tyr Phe Gly Leu Phe Phe Phe Val Ile Ser 275 280 285

Leu Thr Ile Leu Ser Phe Ala Thr Ser Asn Trp His Val Val 290 295 300

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<211> 568

<212> DNA

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<223> RXA00858

<400> 185

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tcttaaattg tctaaccaag aaccggaggt tctttttgtc atg gaa gta aac tta 115
Met Glu Val Asn Leu

gcc aca tgg cta atc act atc gca gtg att gct ggc ttc ttc att ttc 163
Ala Thr Trp Leu Ile Thr Ile Ala Val Ile Ala Gly Phe Phe Ile Phe
10 15 20

gat ttc tat tcc cac gtc cgc acc cca cac gag ccc act atc aaa gaa 211
Asp Phe Tyr Ser His Val Arg Thr Pro His Glu Pro Thr Ile Lys Glu
25 30 35

tcc gca tgg tgg agc ctc ttc tac gta gcc ctc gcc tgt gtt ttc ggc 259 Ser Ala Trp Trp Ser Leu Phe Tyr Val Ala Leu Ala Cys Val Phe Gly

gtg ttc ctc tgg ttt gct tgg ggc gag cca ggt aac cca cac cag cac 307
Val Phe Leu Trp Phe Ala Trp Gly Glu Pro Gly Asn Pro His Gln His
55 60 65

ggc att gag ttc ttc acc ggt tac gtg aca gag aag gcg ttg agt gtt 355 Gly Ile Glu Phe Phe Thr Gly Tyr Val Thr Glu Lys Ala Leu Ser Val 70 75 80 85

gat aac ctc ttc atc ttc gcg ctg atc atg ggt tct ttc aag att cct 403 Asp Asn Leu Phe Ile Phe Ala Leu Ile Met Gly Ser Phe Lys Ile Pro ٩n

				9,	J				Э.	,				100	,	
				g cad n Gli 5					ı Ile					Ala		
			j Lei	g gca u Ala				ı Ala					Ile			
		Asp		c tto L Phe			Phe					Ile				
	. Lys			gtg Val		Glu										568
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Gly	Phe	Phe	11e 20	Phe	Asp	Phe	Tyr	Ser 25	His	Val	Arg	Thr	Pro 30	His	Glu	
Pro	Thr	Ile 35		Glu	Ser	Ala	Trp 40	Trp	Ser	Leu	Phe	Tyr 45	Val	Ala	Leu	
Ala	Cys 50	Val	Phe	Gly	Val	Phe 55	Leu	Trp	Phe	Ala	Trp 60	Gly	Glu	Pro	Gly	
Asn 65	Pro	His	Gln	His	Gly 70	Ile	Glu	Phe	Phe	Thr 75	Gly	Tyr	Val	Thr	Glu 80	
Lys	Ala	Leu	Ser	Val 85	Asp	Asn	Leu	Phe	Ile 90	Phe	Ala	Leu	Ile	Met 95	Gly	
Ser	Phe	Lys	Ile 100	Pro	Arg	Lys	Tyr	Gln 105	Gln	Lys	Val	Leu	Leu 110	Ile	Gly	
Ile	Ala	Leu 115	Ala	Leu	Val	Phe	Arg 120	Leu	Ala	Phe	Ile	Leu 125	Ala	Gly	Ala	
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Leu Ile Tyr Thr Ala Val Lys Ala Pro Val His Glu

<210> 187

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307

355

403

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595

643

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Thr Ser Val Trp His Glu Leu Thr Thr Val Ser Lys Tyr Ser Glu Ala

atc gat ttc tac ggt gag ctg ttc act tgg aca acc tct gaa atg gct Ile Asp Phe Tyr Gly Glu Leu Phe Thr Trp Thr Thr Ser Glu Met Ala

agt gct gaa gac gat agt ttc cgc tac acc acc gca ttg gct gac ggt

140

155

135

WO 01/00804 PCT/IB00/00922

Ser	Ala	Glu	Asp	Asp 170			Arg	Tyr	Thr 175		Ala	Leu	Ala	ASP 180	Gly	
tcc Ser	gcc Ala	ttt Phe	gct Ala 185	Gly	att Ile	ttt Phe	gat Asp	gcc Ala 190	aaa Lys	Gly	cac His	ttc Phe	cca Pro 195	cct Pro	cag Gln	691
gtt Val	cca Pro	agc Ser 200	ttc Phe	tgg Trp	cag Gln	tcc Ser	tac Tyr 205	ctt Leu	ggc Gly	gtg Val	ctc Leu	aac Asn 210	gcc Ala	gat Asp	gat Asp	739
gct Ala	gca Ala 215	gcg Ala	aag Lys	gcc Ala	aag Lys	gaa Glu 220	ttt Phe	ggt Gly	ggc Gly	gat Asp	gtt Val 225	att Ile	cgt Arg	aag Lys	cca Pro	787
												gat Asp				835
												gag Glu				883
gaa Glu	ggc Gly	gat Asp	gat Asp 265	ctc Leu	ttc Phe	gac Asp	atc Ile	gat Asp 270	ctc Leu	agt Ser	gct Ala	ttc Phe	gaa Glu 275	gag Glu	cag Gln	931
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<211> 284

<212> PRT

<213> Corynebacterium glutamicum

<400> 188

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Gly Trp Glu Ile Glu Glu Val Asn Asp Gly Tyr Arg Met Ala Arg Leu 35 40 45

Gln Gly Leu Pro Val Ala Gly Leu Ile Asp Gln Arg Gly Glu Ser Ser 50 55 60

Ile Pro Asp Thr Trp Ile Thr Tyr Phe Leu Ser Tyr Asp Leu Asp Ala 65 70 75 80

Thr Ala Lys Lys Ile Ala Glu Leu Gly Gly Arg Ile Leu Ala Glu Pro 85 90 95

Thr Asp Val His Leu Gly Arg Met Ile Leu Ala Val Asp Thr Ala Gly

P

110

Ala Leu Phe Gly Val Ile Glu Pro Gly Ser Glu Glu Ser Phe Val Ala 115 120 125

Ala Gly Glu Pro Gly Thr Ser Val Trp His Glu Leu Thr Thr Val Ser 130 135 140

Lys Tyr Ser Glu Ala Ile Asp Phe Tyr Gly Glu Leu Phe Thr Trp Thr 145 150 155 160

Thr Ser Glu Met Ala Ser Ala Glu Asp Asp Ser Phe Arg Tyr Thr Thr 165 170 175

Ala Leu Ala Asp Gly Ser Ala Phe Ala Gly Ile Phe Asp Ala Lys Gly
180 185 190

His Phe Pro Pro Gln Val Pro Ser Phe Trp Gln Ser Tyr Leu Gly Val 195 200 205

Leu Asn Ala Asp Asp Ala Ala Ala Lys Ala Lys Glu Phe Gly Gly Asp 210 215 220

Val Ile Arg Lys Pro Trp Asp Ser Glu Phe Gly Arg Met Val Leu Ile 225 230 235 240

Ser Asp Ser Thr Gly Ala Thr Ile Thr Leu Cys Glu Val Glu Glu Tyr 245 250 255

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Ala Phe Glu Glu Gln Phe Arg Lys Gln Glu Gly Gln 275 280

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<211> 948

<212> DNA

<213> Corynebacterium glutamicum

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<223> RXA00084

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Met Ser Thr Ala Leu

1

ccc gat cag ctc aag tgg gaa tac agt gcc ttc ccc gtg cag atc tcg 163 Pro Asp Gln Leu Lys Trp Glu Tyr Ser Ala Phe Pro Val Gln Ile Ser 10 15 20

883

att cgc aaa gaa cta atc aac agc tac cga gtt gat tcc tca cga atc

Ile Arg Lys Glu Leu Ile Asn Ser Tyr Arg Val Asp Ser Ser Arg Ile 250 255 260

act ttc ctc ggc tac tgg aaa tac ggc cga cga acc gta gac Thr Phe Leu Gly Tyr Trp Lys Tyr Gly Arg Arg Thr Val Asp 265 270 275 925

tagctttcag attcagaccc cag

948

<210> 190

<211> 275

<212> PRT

<213> Corynebacterium glutamicum

<400> 190

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Pro Val Gln Ile Ser Gln Lys Gln Arg Leu Ser Pro Gly Phe Met Arg
20 25 30

Ile Thr Val Thr Gly Asp Lys Leu Arg Phe Phe Gly Gln Trp Gly Leu
35 40 45

Asp Gln Arg Ile Lys Leu Ile Ile Pro Ser Pro Ala Gly Asn Ile Pro 50 55 60

Asp Phe Gly Ile Leu Asp Glu Pro Thr Pro Pro Pro Thr Thr Trp Leu 65 70 75 80

Pro Arg Ala Lys Ser Phe Pro Ala Asp Gln Arg Pro Ile Leu Arg Thr 85 90 95

Tyr Thr Pro Ser Ala Val Arg Pro Glu Leu Cys Glu Val Asp Ile Asp 100 105 110

Ile Tyr Leu His Asn Pro Ser Gly Pro Val Ser Arg Trp Ala Lys Asn 115 120 125

Cys Ser Val Asp Asp Glu Leu Ile Ile Thr Gly Pro Asp Val Arg Ala 130 135 140

Gly Glu Thr Gly Tyr Gly Ile Thr Tyr His Pro Thr Ser Ala Ile Asp 145 150 155 160

Arg Leu Cys Leu Ile Gly Asp Cys Ala Ser Ala Pro Ala Ile Ala Asn 165 170 175

Ile Val Asn Gln Ser Lys Val Pro Thr Thr Val Phe Leu His Val Asp 180 185 190

Ser Leu Glu Asp Asp Val Leu Ile Ala Asp Ser Ser Thr Lys Leu Thr 195 200 205

Phe Glu Asp Ile Asp Ala Tyr Lys Ala Lys Val Phe Gln Trp Ala Ser 210 215 220

Ala Asn Ala Ala Asp Pro Ser Val His Phe Trp Ile Ala Gly Glu Thr 230 235 Ser Met Val Arg Phe Ile Arg Lys Glu Leu Ile Asn Ser Tyr Arg Val 250 Asp Ser Ser Arg Ile Thr Phe Leu Gly Tyr Trp Lys Tyr Gly Arg Arg Thr Val Asp . 275 <210> 191 <211> 468 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (101)..(445) <223> RXA00843 <400> 191 gccctgatgc gaaaccggcg ccaacaatga tgccgacgaa ggcaaatgcc actcttagga 60 tttgaataat catggaacaa accttagtag gctcaacgtt atg aaa gtc acg att 115 Met Lys Val Thr Ile 163 tto cat aat dog ogt tgt too aca too aga aat acc oto got tad oto Phe His Asn Pro Arg Cys Ser Thr Ser Arg Asn Thr Leu Ala Tyr Leu 10 211 cgc gac aag gac att gag cct gaa att gtt cag tat ctc aaa gac acg Arg Asp Lys Asp Ile Glu Pro Glu Ile Val Gln Tyr Leu Lys Asp Thr 30 259 ccc acc gct tcc gag ctc aaa gaa cta ttc aat acg ctg ggà att cca Pro Thr Ala Ser Glu Leu Lys Glu Leu Phe Asn Thr Leu Gly Ile Pro 45 gtc cac gac ggc atc aga acc cgc gaa gct gag tac aca gaa ctg ggc 307 Val His Asp Gly Ile Arg Thr Arg Glu Ala Glu Tyr Thr Glu Leu Gly 355 ctg tca cca gaa aca cct gaa act gag ctt atc gac gcc atc gtt gcc Leu Ser Pro Glu Thr Pro Glu Thr Glu Leu Ile Asp Ala Ile Val Ala 70 75 80 403 cat ccc agg ctc ctt cag cgt ccg atc gtg gtg acg gcc aaa ggc gcg His Pro Arg Leu Gln Arg Pro Ile Val Val Thr Ala Lys Gly Ala 100 90 cgc att gcg cgc ccc aaa atc gac gtc att gac agc atc ttg 445 Arg Ile Ala Arg Pro Lys Ile Asp Val Ile Asp Ser Ile Leu

110

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468

<210> 192

<211> 115

<212> PRT

<213> Corynebacterium glutamicum

<400> 192

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Thr Leu Ala Tyr Leu Arg Asp Lys Asp Ile Glu Pro Glu Ile Val Gln

Tyr Leu Lys Asp Thr Pro Thr Ala Ser Glu Leu Lys Glu Leu Phe Asn

Thr Leu Gly Ile Pro Val His Asp Gly Ile Arg Thr Arg Glu Ala Glu

Tyr Thr Glu Leu Gly Leu Ser Pro Glu Thr Pro Glu Thr Glu Leu Ile

Asp Ala Ile Val Ala His Pro Arg Leu Gln Arg Pro Ile Val Val

Thr Ala Lys Gly Ala Arg Ile Ala Arg Pro Lys Ile Asp Val Ile Asp

Ser Ile Leu 115

<210> 193

<211> 432

<212> DNA

<213> Corynebacterium glutamicum

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<222> (101)..(409)

<223> RXA01052

<400> 193

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acgaacaacg aagagcttgc ccgagagtat cttgggtcgc atg gac aca aaa tta Met Asp Thr Lys Leu

ggc gct gaa ttg ggt act gaa ttt gat ctc att gtt ggt ttc ggc 163 Gly Ala Glu Leu Gly Thr Glu Phe Asp Leu Ile Val Val Gly Phe Gly 10 15

WO 01/00804 PCT/IB00/00922 aaa gca ggc aag act atc gcg atg aaa cgc tcg gca gcg ggg gat aag Lys Ala Gly Lys Thr Ile Ala Met Lys Arg Ser Ala Ala Gly Asp Lys qtc qca ctg atc gag cag agt cca cag atg tat ggc ggt acc tqc atc 259 Val Ala Leu Ile Glu Gln Ser Pro Gln Met Tyr Gly Gly Thr Cys Ile 45 aat gta ggt tgc atc ccc acg aag aag ttg ttg ttt gag act gca acg 307 Asn Val Gly Cys Ile Pro Thr Lys Lys Leu Leu Phe Glu Thr Ala Thr gge aag gat tte eeg gat geg gtt gtg geg egt gat eag ttg att gge 355 Gly Lys Asp Phe Pro Asp Ala Val Val Ala Arg Asp Gln Leu Ile Gly 80 aag ctg aat gcc aag aat ctt gcg atg gcc aca gac aag ggt gtc acc Lys Leu Asn Ala Lys Asn Leu Ala Met Ala Thr Asp Lys Gly Val Thr cgt cat tgatggaaaa gctacgttta cag 432 Arg His <210> 194 <213> Corynebacterium glutamicum

<211> 103 <212> PRT

<400> 194

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Val Val Gly Phe Gly Lys Ala Gly Lys Thr Ile Ala Met Lys Arg Ser

Ala Ala Gly Asp Lys Val Ala Leu Ile Glu Gln Ser Pro Gln Met Tyr 35

Gly Gly Thr Cys Ile Asn Val Gly Cys Ile Pro Thr Lys Lys Leu Leu

Phe Glu Thr Ala Thr Gly Lys Asp Phe Pro Asp Ala Val Ala Arg

Asp Gln Leu Ile Gly Lys Leu Asn Ala Lys Asn Leu Ala Met Ala Thr

Asp Lys Gly Val Thr Arg His 100

<210> 195

<211> 543

<212> DNA

<213> Corynebacterium glutamicum

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ago	cacg	aaa	tcac	aagt	aa c	ttca	ggta	g tg	acac	tctt				gcg Ala		115
					Thr					Val				gtc Val 20		163
				Pro					Ser					cac His		211
														atc Ile		259
														acc Thr		307
														gta Val		355
														ctc Leu 100		403
														ctc Leu		451
gac Asp	cac His	gac Asp 120	ctc Leu	ctc Leu	gcc Ala	gac Asp	gcc Ala 125	gca Ala	ctt Leu	ttt Phe	gca Ala	tcg Ser 130	gcc Ala	gac Asp	gcc Ala	499
	cac His 135						tgaa	cagg	ica d	gcat	caaa	a Ca	ıg			543
)> 19 > 14															

<212> PRT

<213> Corynebacterium glutamicum

<400> 196

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	Gly	Ile	Gln 35		: Ile	Ser	Pro	Leu 40		Lys	His	Leu	Ala 45		Ile	Gly	
	Gly	Gly 50		Ile	: Gly	Leu	Glu 55		Ala	Thr	Leu	Phe 60		Gly	Gln	Gly	
	Ser 65	_	Val	Thr	Ile	Ile 70	Asp	Arg	Gly	Glu	Leu 75		Leu	Lys	Asn	Phe 80	
	Asp	Arg	Glu	Val	Ala 85		Leu	Ala	Lys	Thr 90		Leu	Glu	Ala	Arg 95	Gly	
	Ile	Thr	Phe	Leu 100	Asn	Asn	Ala	Glu	Leu 105		Gly	Phe	Ser	Gly 110		Leu	
	Thr	Ile	Ala 115	Leu	Lys	Asp	His	Asp 120	Leu	Leu	Ala	Asp	Ala 125	Ala	Leu	Phe	
	Ala	Ser 130		Asp	Ala	Arg	His 135	Arg	Arg	Ala	Arg	Pro 140					
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					aac Asn 10												163
Ç	ggc Gly	ggc Gly	ccg Pro	cag Gln 25	ttt Phe	acc Thr	tac Tyr	gtg Val	tcc Ser 30	tac Tyr	gat Asp	gac Asp	cac His	cgc Arg 35	att Ile	gtg Val	211
					gcc Ala												259
ē	atc	ccc	acc	acc	acg	ttc	atc	gaa	ccg	ccg	tta	tcc	acc	atc	ggt	gac	307

Ile Pro Thr Thr Thr Phe Ile Glu Pro Pro Leu Ser Thr Ile Gly Asp 60 aac act gaa ggg gaa aat gtg gtg gtg aaa aag gcc ttg att gca gat 355 Asn Thr Glu Gly Glu Asn Val Val Val Lys Lys Ala Leu Ile Ala Asp 80 403 atg ccq atc gtt ccc cga cca gag att att aac caa cct cac ggt atg Met Pro Ile Val Pro Arg Pro Glu Ile Ile Asn Gln Pro His Gly Met gtg aag ttt ttc gtc gac aag caa tct gat gcg ctg ctc ggc gcg acc 451 Val Lys Phe Phe Val Asp Lys Gln Ser Asp Ala Leu Leu Gly Ala Thr ttg tac tgc gcc gac tcc cag gag ctc atc aac acc gtg gcg ctt gcc 499 Leu Tyr Cys Ala Asp Ser Gln Glu Leu Ile Asn Thr Val Ala Leu Ala 130 125 547 atg cgg cat ggc gtc acc gcc tcc gag ctt ggc gac ggc atc tac acc Met Arg His Gly Val Thr Ala Ser Glu Leu Gly Asp Gly Ile Tyr Thr 140 589 cac ccc gcc acc tcg gag atc ttc aac caa tta ttg ggc agt His Pro Ala Thr Ser Glu Ile Phe Asn Gln Leu Leu Gly Ser 160 612 taacgcagcg gatcgaacgg ctt <210> 198 <211> 163 <212> PRT <213> Corynebacterium glutamicum <400> 198 Val Leu Val Asp Ala His Leu Arg Thr Asn Ile Asp Gly Ile Phe Ala Val Gly Asp Val Asn Gly Gly Pro Gln Phe Thr Tyr Val Ser Tyr Asp Asp His Arg Ile Val Leu Asp Gln Leu Ala Gly Thr Gly Lys Lys Ser Ile Ala His Arg Leu Ile Pro Thr Thr Thr Phe Ile Glu Pro Pro Leu Ser Thr Ile Gly Asp Asn Thr Glu Gly Glu Asn Val Val Lys Lys Ala Leu Ile Ala Asp Met Pro Ile Val Pro Arg Pro Glu Ile Ile Asn Gln Pro His Gly Met Val Lys Phe Phe Val Asp Lys Gln Ser Asp Ala

105

100

Leu Leu Gly Ala Thr Leu Tyr Cys Ala Asp Ser Gln Glu Leu Ile Asn 115 120 125

Thr Val Ala Leu Ala Met Arg His Gly Val Thr Ala Ser Glu Leu Gly 130 135 140

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Val Gly Asp Ala Leu
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gcc atc cca gat cca gcg ccg cgt ggc ttc ctt ttc tta ggc gat ctc 211
Ala Ile Pro Asp Pro Ala Pro Arg Gly Phe Leu Phe Leu Gly Asp Leu
25 30 35

acc tot tac oca gog ato tgo tog att otg gag acc ttg gac ggt gaa 259
Thr Ser Tyr Pro Ala Ile Cys Ser Ile Leu Glu Thr Leu Asp Gly Glu
40 45 50

atc cct gcg acc gcg tat ctt atc gcc cac gat cca ctt gat tac acc

Ile Pro Ala Thr Ala Tyr Leu Ile Ala His Asp Pro Leu Asp Tyr Thr

55 60 65

ttc gat ttt ccc cag ggc gag cac atc acc gcg cag tgg att tcc aac
Phe Asp Phe Pro Gln Gly Glu His Ile Thr Ala Gln Trp Ile Ser Asn
70 75 80 85

gaa caa too tto att gat cac atc got gac acg gat tac acc gat ttt 403 Glu Gln Ser Phe Ile Asp His Ile Ala Asp Thr Asp Tyr Thr Asp Phe

tat acc tgg atc ggc gcg gaa tcc tcc gaa acc cgt gcg gcc aag aag 451 Tyr Thr Trp Ile Gly Ala Glu Ser Ser Glu Thr Arg Ala Ala Lys Lys 105 110 115

499 cat ctg cag acc cac gcc ggc atg ccc aag acg cac atg aac gcg caa His Leu Gln Thr His Ala Gly Met Pro Lys Thr His Met Asn Ala Gln 120 ggt tat tgg aac aag ggc aga gcc atg ggt aaa agc aat taaaagattt 548 Gly Tyr Trp Asn Lys Gly Arg Ala Met Gly Lys Ser Asn 561 ttgcttatcg acg <210> 200 <211> 146 <212> PRT <213> Corynebacterium glutamicum <400> 200 Val Gly Asp Ala Leu Arg Gly Arg Gly Lys Pro Glu Val Met Arg Tyr Pro Gly Ile Pro Phe Ala Ile Pro Asp Pro Ala Pro Arg Gly Phe Leu 25 Phe Leu Gly Asp Leu Thr Ser Tyr Pro Ala Ile Cys Ser Ile Leu Glu Thr Leu Asp Gly Glu Ile Pro Ala Thr Ala Tyr Leu Ile Ala His Asp 55 Pro Leu Asp Tyr Thr Phe Asp Phe Pro Gln Gly Glu His Ile Thr Ala Gln Trp Ile Ser Asn Glu Gln Ser Phe Ile Asp His Ile Ala Asp Thr 95 Asp Tyr Thr Asp Phe Tyr Thr Trp Ile Gly Ala Glu Ser Ser Glu Thr Arg Ala Ala Lys Lys His Leu Gln Thr His Ala Gly Met Pro Lys Thr His Met Asn Ala Gln Gly Tyr Trp Asn Lys Gly Arg Ala Met Gly Lys 135 130

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Thr Asp Phe Tyr Thr Trp Ile Gly Ala Glu Ser Ser Glu Thr Arg
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Val Thr Ile His Phe His Ser Glu Thr Leu Leu Asn Thr Glu Gly Glu 35 40 45

Val Pro Gly Asp Trp Leu Arg Leu Trp Phe Pro His Glu Ser Arg Pro 50 55 60

Gly Lys Leu Tyr Gln Arg Ala Tyr Thr Leu Thr Asn Val Asp Ala Asp 65 70 75 80

Ala Gly Thr Phe Asp Leu Ala Phe Val Leu His Glu Pro Leu Gly Pro 85 90 95

Ala Ser Ala Trp Ala Thr Arg Cys Glu Ala Gly Glu Ser Leu Glu Val

Met Arg Tyr Pro Gly Ile Pro Phe Ala Ile Pro Asp Pro Ala Pro Arg 115 120 125

Gly Phe Leu Phe Leu Gly Asp Leu Thr Ser Tyr Pro Ala Ile Cys Ser 130 135 140

Ile Leu Glu Thr Leu Asp Gly Glu Ile Pro Ala Thr Ala Tyr Leu Ile 145 150 155 160

Ala His Asp Pro Leu Asp Tyr Thr Phe Asp Phe Pro Gln Gly Glu His
165 170 175

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Ser Glu Thr Arg 210

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agc gga atc atc atg ggc ggt tca cta tct gtg atg gcg atg atg atg Ser Gly Ile Ile Met Gly Gly Ser Leu Ser Val Met Ala Met Met Met

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Phe Asn Ala Ser Ser Leu Leu Phe Ala Phe Ser Phe Gly Val Tyr Leu 35 40 45

Val Leu Leu Val Met Met Thr Leu Leu Lys Ser Arg Leu Ser Leu Gly 50 55 60

Gly Leu Trp Asn Thr Glu Ala His Gln Tyr Arg Ser Ile Asp Leu Glu
65 70 75 80

Leu Phe Asn Gly Phe Ala Asp Pro Pro Ile Trp Trp Gly Pro Trp Thr 85 90 95

Asn Thr Phe Gly Asn Ile Ala Leu Phe Met Pro Phe Gly Phe Phe Leu 100 105 110

Tyr Lys Met Leu Arg Arg Phe Asn His Arg Phe Pro Phe Val Glu Thr 115 120 125

Ile Leu Phe Ala Ser Val Thr Ser Leu Ser Ile Glu Val Leu Gln Trp 130 135 140

Val Phe Ala Ile Gly Tyr Ser Asp Val Asp Asp Leu Leu Phe Asn Thr 145 150 155 160

Ile Gly Gly Leu Ile Gly Ala Ser Val Ala Ala Leu Val Ser Leu Lys 165 170 175

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gat agc aag gtc (Asp Ser Lys Val (gag gca cac ga Glu Ala His Gl 10	a ggc cac gaa u Gly His Glu 15	Gly His Gin G.	gc atc 163 ly Ile 20
gag cga gga aca d Glu Arg Gly Thr A 25	cgc aat tac aa Arg Asn Tyr Ly	g cgc gct gtg s Arg Ala Val 30	ttt gcg atg c Phe Ala Met L 35	tg gcc 211 eu Ala
gcc ggt ctt gct g Ala Gly Leu Ala A	Ala Phe Asn Gl	t ctt tat tgc y Leu Tyr Cys 5	acg cag gca t Thr Gln Ala L 50	tg ctt 259 eu Leu
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tcg ata ctt tcg (Ser Ile Leu Ser (gag aaa ttt gg Glu Lys Phe Gl 90	t cgc ggt cgg y Arg Gly Arg 95	Val Leu Thr 1	tt tca 403 le Ser 00
ctc acg ttg gcc a Leu Thr Leu Ala 1	atc atc gtg gg Ile Ile Val Gl	a tta att ttg y Leu Ile Leu 110	ccg ctt gtc c Pro Leu Val P 115	cc aat 451 ro Asn
att act gct ctc a Ile Thr Ala Leu 1 120	atc ctg ctc ag Ile Leu Leu Ar 12	g Gly Leu Gln	ggt gcg ctg c Gly Ala Leu L 130	tt gct 499 eu Ala
ggc act cca gcg g Gly Thr Pro Ala V 135	gtg gcg atg ac Val Ala Met Th 140	c tgg ttg tct r Trp Leu Ser	gag gaa att c Glu Glu Ile H 145	ac ccc 547 is Pro
aag gat att ggg G Lys Asp Ile Gly H 150	cat gcg atg gg His Ala Met Gl 155	a att tac atc y Ile Tyr Ile 160	gcg gga aat a Ala Gly Asn T	ct gtc 595 hr Val 165

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tct Ser	gga Gly 375	ttc Phe	gcg Ala	ttt Phe	acg Thr	cat His 380	ttg Leu	ccg Pro	tgg Trp	ttg Leu	gcg Ala 385	ttc Phe	att Ile	ggc Gly	tgg Trp	1267
ttg Leu	att Ile	ctg Leu	ctt Leu	ctt Leu	tgc Cys	gga Gly	gtg Val	ctg Leu	gcg Ala	att Ile	tgt Cys	gtg Val	acg Thr	ctg Leu	gca Ala	1315

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Thr Gln Ala Leu Leu Pro Thr Met Thr Glu Glu Leu Gly Ile Thr Pro
50 55 60

Thr Glu Ser Ala Leu Thr Val Ser Ala Thr Thr Gly Met Leu Ala Leu 65 70 75 80

Cys Ile Val Pro Ala Ser Ile Leu Ser Glu Lys Phe Gly Arg Gly Arg 85 90 95

Val Leu Thr Ile Ser Leu Thr Leu Ala Ile Ile Val Gly Leu Ile Leu 100 105 110

Pro Leu Val Pro Asn Ile Thr Ala Leu Ile Leu Leu Arg Gly Leu Gln 115 120 125

Gly Ala Leu Leu Ala Gly Thr Pro Ala Val Ala Met Thr Trp Leu Ser 130 135 140

Glu Glu Ile His Pro Lys Asp Ile Gly His Ala Met Gly Ile Tyr Ile 145 150 155 160

Ala Gly Asn Thr Val Gly Gly Leu Thr Gly Arg Met Ile Pro Ala Gly 165 170 175

Leu Leu Glu Val Thr His Trp Gln Asn Ala Leu Leu Gly Ser Ser Ile 180 185 190

Ala Ala Leu Ile Phe Gly Val Ile Met Val Val Leu Leu Pro Lys Gln 195 200 205

Arg Lys Phe Gln Pro Lys Asn Ile Asn Leu Arg His Glu Ile Ser Ala 210 215 220

Met Ala Ala His Trp Arg Asn Pro Arg Leu Ala Leu Leu Phe Gly Thr 225 230 235 240

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His	Ser	Ser	Ala 340	Ser	Gly	Trp	Ile	Gly 345	Ile	Ile	Ala	Thr	Lys 350	Asp	Arg	
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Ala 385	Phe	Ile	Gly	Trp	Leu 390	Ile	Leu	Leu	Leu	Cys 395	Gly	Val	Leu	Ala	Ile 400	
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gat Asp	agc Ser	aag Lys	gtc Val	gag Glu 10	gca Ala	cac His	gaa Glu	ggc Gly	cac His	gaa Glu	ggc Gly	cac His	gaa Glu	ggc Gly 20	atc Ile	163

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ggc Gly	ggg Gly	ctc Leu	act Thr	gga Gly 170	cgt Arg	atg Met	att Ile	ccg Pro	gcg Ala 175	gga Gly	cta Leu	ctt Leu	gaa Glu	gta Val 180	act Thr	643
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Leu Leu Glu Val Thr His Trp Gln Asn Ala Leu Leu Gly Ser Ser Ile 180 185 190

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Arg Lys Phe Gln Pro Lys Asn Ile Asn Leu Arg His Glu Ile Ser Ala 210 215 220

Met Ala Ala His Trp Arg Asn Pro Arg Leu Ala Leu Leu Phe Gly Thr 225 230 235 240

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Phe Arg Met Ile Asp Gln Phe Gly Leu Ser Glu Val Leu Val Gly Ala 260 265 270

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Leu Thr Met Ile Ala Ser Met Ala Leu Met Gly Ile Asn Asn Leu Trp 305 310 315 320

Val Thr Leu Val Ala Leu Phe Val Phe Thr Ala Ala Phe Phe Ala Leu 325 330 335

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- Ser Leu Thr Phe Leu Ala Val Phe Val Phe Ile Glu Arg Ile Ala Ser 245 250 255
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- Val Val Met Trp Val Gln Gln Met Gly Trp Gly Val Ser Pro Thr Ile 290 295 300
- Ser Gly Leu Thr Ser Ile Gly Phe Ala Ala Phe Val Ile Leu Phe Ile 305 310 315 320
- Arg Val Gly Glu Lys Ala Met Gln Lys Val Gly Ala Arg Ala Val Ile 325 330 335
- Ile Thr Ala Gly Ile Leu Val Ala Thr Ala Thr Ala Leu Leu Met Ile 340 345 350
- Thr Ala Val Ser Glu Ser Thr Tyr Ile Val Ile Ser Leu Ala Gly Phe 355 360 365
- Ser Leu Tyr Gly Leu Gly Leu Gly Leu Phe Ala Thr Pro Val Thr Asp 370 375 380
- Thr Ala Leu Gly Thr Leu Pro Lys Asp Arg Thr Gly Ala Gly Ala Gly 385 390 395 400
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- Ser Thr Ser Val Phe Leu Ala Leu Arg Asp Gly Thr Ser Ile Asn Ser 420 425 430
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Ile Gly Pro Asp Met Ala Thr Asp Leu Gly Met Ser Asp Gly Thr Met 35 40 45

Asn Ile Ala Val Val Ala Ala Ala Leu Phe Cys Gly Thr Phe Ile Val 50 55 60

Ala Ala Gly Gly Ile Ala Asp Val Phe Gly Arg Val Arg Ile Met Met 65 70 75 80

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Val Val Ala Ser Pro Phe Gly Trp Arg Gly Ile Phe Ala Leu Cys Ala 165 170 175

Ile Val Ser Ile Val Ala Ile Ala Leu Thr Arg His Ile Pro Glu Ser 180 185 190

Arg Pro Ala Gln Ser Ile Gly Met His Leu Asp Trp Ser Gly Ile Ile 195 200 205

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Glu Ser Leu Gly Trp Thr His Trp Met Thr Trp Thr Leu Leu Ala Val 225 230 235 240

Ser Leu Thr Phe Leu Ala Val Phe Val Phe Ile Glu Arg Ile Ala Ser 245 250 255

Trp Pro Val Leu Asp Phe Asn Leu Phe Lys Asp His Ala Phe Ser Gly 260 265 270

Ala Thr Ile Thr Asn Phe Ile Met Ser Ala Thr Gly Gly Val Val Ala 275 280 285

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643

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					gat gca	307
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Tyr Asn Gly Asn Val Phe Gly Ala Ala Ala Thr Ser Leu Asp Met Thr
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Thr Thr Glu Asn Lys Lys Ser Gly Pro Pro Arg Leu Met Arg Ile

10

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gtc Val	agc Ser	gat Asp	gaa Glu	ccc Pro 90	tta Leu	aca Thr	cag Gln	caa Gln	gac Asp 95	atc Ile	aca Thr	caa Gln	ctc Leu	aat Asn 100	gaa Glu	403
gtt Val	gtt Val	gct Ala	ggg Gly 105	ctt Leu	tca Ser	gaa Glu	tta Leu	gac Asp 110	ata Ile	gtt Val	tcc Ser	gat Asp	gaa Glu 115	gtc Val	tcc Ser	451
cct Pro	gct Ala	att Ile 120	cca Pro	tcc Ser	gag Glu	gac Asp	ggc Gly 125	aga Arg	gct Ala	gtc Val	caa Gln	gtg Val 130	ttt Phe	gtc Val	ccc Pro	499
ctc Leu	aat Asn 135	cca Pro	tca Ser	gcg Ala	gag Glu	ctg Leu 140	acg Thr	gaa Glu	agc Ser	gtc Val	gag Glu 145	aag Lys	ctc Leu	tct Ser	gag Glu	547
acc Thr 150	ttg Leu	acc Thr	cag Gln	caa Gln	acg Thr 155	ccg Pro	gac Asp	tat Tyr	gtg Val	agc Ser 160	acc Thr	tat Tyr	gtg Val	acc Thr	gga Gly 165	595
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Gly	cta Leu	ctc Leu	cta Leu 185	gca Ala	gtc Val	gcc Ala	ttg Leu	gct Ala 190	gcc Ala	gtc Val	ctt Leu	gtc Val	att Ile 195	ctt Leu	gtc Val	691
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ctc Leu 390	ttg Leu	ggt Gly	gcg Ala	gct Ala	ttc Phe 395	gtt Val	ccc Pro	aca Thr	cta Leu	aaa Lys 400	gcg Ala	gac Asp	ggt Gly	gtg Val	tcc Ser 405	1315
caa Gln	tcc Ser	gac Asp	cta Leu	gtt Val 410	ctg Leu	ggt Gly	tcc Ser	tct Ser	gaa Glu 415	gca Ala	cgt Arg	gat Asp	ggc Gly	cag Gln 420	cag Gln	1363
gct Ala	tta Leu	ggc Gly	gaa Glu 425	cac His	ttc Phe	ccc Pro	ggt Gly	gga Gly 430	tcc Ser	ggc Gly	agt Ser	cct Pro	gct Ala 435	tat Tyr	att Ile	1411
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aca Thr	ctt Leu	gtc Val	gaa Glu 505	gca Ala	cca Pro	gat Asp	tcc Ser	gaa Glu 510	gaa Glu	gct Ala	caa Gln	aaa Lys	gct Ala 515	att Ile	cgc Arg	1651
agt Ser	atc Ile	cgc Arg 520	caa Gln	act Thr	ttt Phe	gca Ala	gat Asp 525	gaa Glu	aat Asn	ata Ile	tca Ser	gcg Ala 530	gta Val	gta Val	ggc Gly	1699
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acc Thr	gtg Val	gtg Val	tct Ser 585	ttt Phe	gct Ala	act Thr	gct Ala	tta Leu 590	ggc Gly	gtg Val	gct Ala	gct Ala	tta Leu 595	ctt Leu	ttc Phe	1891
aat Asn	cac His	gtt Val 600	ttc Phe	agt Ser	ttc Phe	cca Pro	gga Gly 605	gca Ala	gac Asp	ccc Pro	gca Ala	gta Val 610	cct Pro	ctc Leu	tac Tyr	1939
gga Gly	ttt Phe 615	gta Val	ttt Phe	tta Leu	gta Val	gcc Ala 620	ttg Leu	ggc Gly	atc Ile	gac Asp	tac Tyr 625	aac Asn	att Ile	ttc Phe	tta Leu	1987
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gta Val	gtt Val	ctc Leu	gcc Ala 665	gca Ala	acg Thr	ttc Phe	gca Ala	gca Ala 670	ctc Leu	tat Tyr	gtc Val	atc Ile	cca Pro 675	att Ile	cta Leu	2131
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715

2313

2275

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<212> PRT

<213> Corynebacterium glutamicum

<400> 218

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Ser Ser Asn Ser Gln Thr Thr Tyr Leu Pro Glu Ser Ala Asp Ala Thr 55

Gln Val Gln Glu Gln Leu Gly Asp Phe Thr Asp Ser Glu Ser Ile Pro

Ala Ile Val Val Met Val Ser Asp Glu Pro Leu Thr Gln Gln Asp Ile

Thr Gln Leu Asn Glu Val Val Ala Gly Leu Ser Glu Leu Asp Ile Val 105

Ser Asp Glu Val Ser Pro Ala Ile Pro Ser Glu Asp Gly Arq Ala Val 120

Gln Val Phe Val Pro Leu Asn Pro Ser Ala Glu Leu Thr Glu Ser Val

Glu Lys Leu Ser Glu Thr Leu Thr Gln Gln Thr Pro Asp Tyr Val Ser 150 155 145

Thr Tyr Val Thr Gly Pro Ala Gly Phe Thr Ala Asp Leu Ser Ala Ala 170

Phe Ala Gly Ile Asp Gly Leu Leu Leu Ala Val Ala Leu Ala Ala Val

Leu Val Ile Leu Val Ile Val Tyr Arg Ser Phe Ile Leu Pro Ile Ala 200

Val Leu Ala Thr Ser Leu Phe Ala Leu Thr Val Ala Leu Leu Val Val

220

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Leu	Tyr	Val	Ala 260	Arg	Phe	Arg	Glu	Glu 265	Leu	Arg	Val	Gln	Gln 270	Asp	Lys
Gly	Ile	Ala 275	Thr	Gly	Lys	Ala	Ile 280	Arg	Ala	Ser	Val	Glu 285	Pro	Ile	Leu
Ala	Ser 290	Gly	Ser	Thr	Val	Ile 295	Ala	Gly	Leu	Leu	Cys 300	Leu	Leu	Phe	Ser
Asp 305	Leu	Lys	Ser	Asn	Ser 310	Thr	Leu	Gly	Pro	Val 315	Ala	Ser	Val	Gly	11e 320
Ile	Phe	Ala	Met	Leu 325	Ser	Ala	Leu	Thr	Leu 330	Leu	Pro	Ala	Leu	Leu 335	Phe
Val	Phe	Gly	Arg 340	Val	Ala	Phe	Trp	Pro 345	Lys	Arg	Pro	Lys	Tyr 350	Glu	Pro
Glu	Lys	Ala 355	Arg	Ala	Lys	Asn	Asp 360	Ile	Pro	Ala	Ser	Gly 365	Ile	Trp	Ser
Lys	Val 370	Ala	Asp	Leu	Val	Glu 375	Gln	His	Pro	Arg	Ala 380	Ile	Trp	Val	Ser
Thr 385	Leu	Ile	Val	Leu	Leu 390	Leu	Gly	Ala	Ala	Phe 395	Val	Pro	Thr	Leu	Lys 400
Ala	Asp	Gly	Val	Ser 405	Gln	Ser	Asp	Leu	Val 410	Leu	Gly	Ser	Ser	Glu 415	Ala
Arg	Asp	Gly	Gln 420	Gln	Ala	Leu	Gly	Glu 425	His	Phe	Pro	Gly	Gly 430	Ser	Gly
Ser	Pro	Ala 435	Tyr	Ile	Ile	Val	Asp 440	Glu	Thr	Gln	Ala	Ala 445	Gln	Ala	Ala
Asp	Val 450	Val	Leu	Asn	Asn	Asp 455	Asn	Phe	Glu	Thr	Val 460	Thr	Val	Thr	Ser
Ala 465	Asp	Ser	Pro	Ser	Gly 470	Ser	Ala	Pro	Ile	Thr 475	Ala	Asp	Gly	Ile	Val 480
Pro	Leu	Gly	Ser	Gly 485	Thr	Ala	Pro	Gly	Pro 490	Val	Val	Val	Glu	Gly 495	Gln
Val	Leu	Leu	Gln 500	Ala	Thr	Leu	Val	Glu 505	Ala	Pro	Asp	Ser	Glu 510	Glu	Ala
Gln	Lys	Ala	Ile	Arg	Ser	Ile	Arg	Gln	Thr	Phe	Ala	Asp	Glu	Asn	Ile

Ser Ala Val Val Gly Gly Val Thr Ala Thr Ser Val Asp Thr Asn Asp

520

Ala Ser Ile His Asp Arg Asn Leu Ile Ile Pro Ile Val Leu Leu Val 545 550 555 560

Ile Leu Val Ile Leu Met Leu Leu Leu Arg Ser Ile Val Ala Pro Leu 565 570 575

Leu Leu Val Val Thr Thr Val Val Ser Phe Ala Thr Ala Leu Gly Val 580 585 590

Ala Ala Leu Leu Phe Asn His Val Phe Ser Phe Pro Gly Ala Asp Pro 595 600 605

Ala Val Pro Leu Tyr Gly Phe Val Phe Leu Val Ala Leu Gly Ile Asp 610 615 620

Tyr Asn Ile Phe Leu Val Thr Arg Ile Arg Glu Glu Thr Lys Thr His 625 630 635 640

Gly Thr Arg Leu Gly Ile Leu Arg Gly Leu Thr Val Thr Gly Gly Val 645 650 655

Ile Thr Ser Ala Gly Val Val Leu Ala Ala Thr Phe Ala Ala Leu Tyr 660 665 670

Val Ile Pro Ile Leu Phe Leu Ala Gln Ile Ala Phe Ile Val Ala Phe 675 680 685

Gly Val Leu Ile Asp Thr Leu Leu Val Arg Ala Phe Leu Val Pro Ala 690 695 700

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<212> DNA

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<222> (1)..(960)

<223> RXN03124

<400> 219

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ctg Leu	gtt Val	gct Ala	ctg Leu	tcg Ser 85	atc Ile	att Ile	aat Asn	att Ile	cca Pro 90	ttt Phe	cta Leu	acc Thr	gtg Val	atg Met 95	gcc Ala	288
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ttc Phe	ctc Leu	cca Pro 115	gct Ala	ctg Leu	ctt Leu	ggc Gly	ctg Leu 120	ctt Leu	ggc Gly	act Thr	cgc Arg	atc Ile 125	ttc Phe	gca Ala	gca Ala	384
cgc Arg	gtg Val 130	cct Pro	gga Gly	cct Pro	aag Lys	gtt Val 135	ccg Pro	gat Asp	cct Pro	gag Glu	gac Asp 140	gag Glu	aag Lys	cca Pro	acg Thr	432
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cgc Arg	aac Asn 210	gcg Ala	ccc Pro	atg Met	att Ile	gcg Ala 215	ctt Leu	atc Ile	gac Asp	gca Ala	acc Thr 220	gac Asp	gtc Val	cct Pro	gag Glu	672
gaa Glu 225	gaa Glu	cgc Arg	cca Pro	ttg Leu	gtg Val 230	ttt Phe	gga Gly	cag Gln	gcg Ala	gtg Val 235	gag Glu	caa Gln	ttc Phe	ttg Leu	aac Asn 240	720
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135

150

Met Gly Leu Lys Trp Val Arg Leu Val Arg Lys Met Pro Val Ala Tyr

130

155

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Leu	Leu	Val	Gly	Val 165	Val	Leu	Leu		Ala 170	Ile	Ala	Ile	Pro	Ala 175	Thr
		_	•		N- L		m L	N	C1	m L	C	mb	LOU	G1.,	Thr

Asn Met Arg Leu Ala Met Pro Thr Asp Gly Thr Ser Thr Leu Gly Thr 180 185 190

Ala Pro Arg Thr Gly Tyr Asp Met Thr Ala Asp Ala Phe Gly Pro Gly 195 200 205

Arg Asn Ala Pro Met Ile Ala Leu Ile Asp Ala Thr Asp Val Pro Glu 210 215 220

Glu Glu Arg Pro Leu Val Phe Gly Gln Ala Val Glu Gln Phe Leu Asn 225 230 235 240

Thr Asp Gly Val Lys Asn Ala Gln Ile Thr Gln Thr Thr Glu Asn Phe 245 250 255

Asp Thr Ala Gln Ile Leu Leu Pro Gln Asn Leu Met Arg Ser Met Ser 260 265 270

Ala Pro Leu Arg Leu Ser Gln Leu Phe Val Gln Met Leu Arg Pro Ser 275 280 285

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<222> (1)..(762)

<223> FRXA01180

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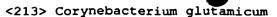
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Thr Gly Ala Asn Asp Leu Glu Pro Lys Glu Leu Ala Glu Arg Leu Arg
35 40 45

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gcg Ala	ccg Pro	cgc Arg 195	acg Thr	ggg Gly	tat Tyr	gac Asp	atg Met 200	acg Thr	gca Ala	gat Asp	gcg Ala	ttc Phe 205	Gj y ggc	ccg Pro	ggc Gly	624
cgc Arg	aac Asn 210	gcg Ala	ccc Pro	atg Met	att Ile	gcg Ala 215	ctt Leu	atc Ile	gac Asp	gca Ala	acc Thr 220	gac Asp	gtc Val	cct Pro	gag Glu	672
gaa Glu 225	gaa Glu	cgc Arg	cca Pro	ttg Leu	gtg Val 230	ttt Phe	gga Gly	cag Gln	gcg Ala	gtg Val 235	gag Glu	caa Gln	ttc Phe	ttg Leu	aac Asn 240	720
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35 40 45

Thr Met Pro Leu Ala Ala Arg Ala His Ala Met Gly Met Ala Val Gly 50 55 60

Thr Ala Gly Ser Ala Val Val Phe Ala Gly Thr Thr Val Leu Ile Ala 65 70 75 80

Leu Val Ala Leu Ser Ile Ile Asn Ile Pro Phe Leu Thr Val Met Ala 85 90 95

Ile Ala Ala Ile Thr Val Ala Ile Ala Val Leu Val Ala Leu Ser 100 105 110

Phe Leu Pro Ala Leu Leu Gly Leu Leu Gly Thr Arg Ile Phe Ala Ala 115 120 125

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Met Gly Leu Lys Trp Val Arg Leu Val Arg Lys Met Pro Val Ala Tyr 145 150 155 160

Leu Leu Val Gly Val Val Leu Leu Gly Ala Ile Ala Ile Pro Ala Thr 165 170 175

Asn Met Arg Leu Ala Met Pro Thr Asp Gly Thr Ser Thr Leu Gly Thr 180 185 190

Ala Pro Arg Thr Gly Tyr Asp Met Thr Ala Asp Ala Phe Gly Pro Gly
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Arg Asn Ala Pro Met Ile Ala Leu Ile Asp Ala Thr Asp Val Pro Glu 210 215 220

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- Leu Ala Leu Thr Val Pro Leu Thr Gly Val Lys Phe Gly Gly Ile Asn
- Glu Thr Tyr Leu Pro Pro Ala Asn Asp Thr Arg Val Ala Gln Glu Arg
- Phe Asp Glu Ala Phe Pro Ala Phe Arg Thr Glu Pro Val Lys Leu Val 420 425

Val Thr Gly Ala Asp Asn Asn Gln Leu Ile Asp Ile Tyr Val Gln Ala 435 440 445

Asn Glu Val Glu Gly Leu Thr Asp Arg Phe Thr Ala Gly Ala Thr Thr 450 455 460

Asp Asp Gly Thr Thr Val Leu Ser Thr Gly Ile Gln Asp Arg Ser Leu 465 470 475 480

Asn Glu Gln Val Val Glu Gln Leu Arg Ala Ile Ser Val Pro Glu Gly 485 490 495

Val Glu Val Gln Ile Gly Gly Thr Pro Ala Met Glu Ile Glu Ser Ile 500 505 510

Glu Ala Leu Phe Glu Lys Leu Leu Trp Met Ala Leu Tyr Ile Val Leu 515 520 525

Ala Thr Phe Ile Leu Met Ala Leu Val Phe Gly Ser Val Ile Leu Pro 530 535 540

Ala Lys Ala Ile Ile Met Thr Ile Leu Gly Met Gly Ala Thr Leu Gly 545 550 560

Ile Leu Thr Leu Met Phe Val Asp Gly Val Gly Ala Ser Ala Leu Asn 565 570 575

Phe Ser Pro Gly Pro Leu Met Ser Pro Val Leu Val Leu Ile Met Ala 580 585 590

Ile Ile Tyr Gly Leu Ser Thr Asp Tyr Glu Val Phe Leu Val Ser Arg 595 600 605

Met Val Glu Ala Arg Asp Lys Gly Glu Ser Thr Asp Asp Ala Ile Arg

Tyr Gly Thr Ala His Thr Gly Ser Ile Ile Thr Ala Ala Ala Leu Ile 625 630 635 640

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Lys Tyr Ile Ala Phe Gly Met Ile Ala Ala Leu Ile Leu Asp Ala Thr 660 665 670

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729

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Phe Gly Ala Thr Val Ala Ile Phe Gln Glu Gly Ala Phe Gly Ile Ile 35 40 45

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Leu Val Phe Gly Leu Ala Met Asp Tyr Gln Ile Phe Leu Val Thr Arg 65 70 75 80

Met Arg Glu Gly Phe Thr Lys Gly Lys Thr Ala Gly Asn Ala Thr Ser 85 90 95

Asn Gly Phe Lys His Gly Ala Arg Val Val Thr Ala Ala Ala Leu Ile 100 105 110

Met Val Ser Val Phe Ala Ala Phe Ile Ala Gln Asp Met Ala Phe Ile 115 120 125

Lys Thr Met Gly Phe Ala Leu Ala Val Ala Val Phe Phe Asp Ala Phe 130 135 140

Val Val Arg Met Met Ile Ile Pro Ala Thr Met Phe Leu Leu Asp Asp 145 150 155 160

Lys Ala Trp Trp Leu Pro Lys Trp Leu Asp Lys Ile Leu Pro Asn Val

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175

150

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act Thr 230	gca Ala	cgc Arg	cat His	atg Met	cct Pro 235	ctt Leu	ctt Leu	ttg Leu	ggt Gly	gca Ala 240	gtc Val	atc Ile	atg Met	ttg Leu	atc Ile 245	835
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ctt Leu	cta Leu	gat Asp	ctg Leu 265	tcg Ser	ttg Leu	ttc Phe	cgt Arg	aat Asn 270	cgc Arg	ctt Leu	ttc Phe	tta Leu	ggc Gly 275	ggt Gly	gtg Val	931
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ggt Gly	ggt Gly	ttt Phe	gct Ala 345	gcc Ala	act Thr	gcc Ala	gtt Val	ggc Gly 350	atc Ile	gcc Ala	ctg Leu	tgt Cys	att Ile 355	tgg Trp	ggc Gly	1171
gcg Ala	act Thr	cat His 360	act Thr	gat Asp	ggt Gly	ttg Leu	ccg Pro 365	ttt Phe	ttc Phe	atc Ile	gcg Ala	ggt Gly 370	cta Leu	ttc Phe	ttc Phe	1219
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atc	ggt	tcc	gcg	ccg	gtg	cgt	aag	gct	ggc	atg	gcg	tcg	tcg	atc	gaa	1315

Ile Gly Ser Ala Pro Val Arg Lys Ala Gly Met Ala Ser Ser Ile Glu 395 gag gtc tct tat gag ttc ggc acg ctg ttg tct gtc gcg att ttg ggt 1363 Glu Val Ser Tyr Glu Phe Gly Thr Leu Leu Ser Val Ala Ile Leu Gly 410 ago ttg tto oca tto tto tac tog ctg cat god cog goa gag gtt gog 1411 Ser Leu Phe Pro Phe Phe Tyr Ser Leu His Ala Pro Ala Glu Val Ala 1459 gat aac ttc tog gog ggt gtt cac cac gog att gat ggc gat gog gog Asp Asn Phe Ser Ala Gly Val His His Ala Ile Asp Gly Asp Ala Ala 445 1507 cgt gca tct ttg gac acc gca tac att aac gtg ttg atc att gcc cta Arg Ala Ser Leu Asp Thr Ala Tyr Ile Asn Val Leu Ile Ile Ala Leu 460 gta tgc gca gta gcg gct gct ctg atc agc agt tac ctt ttc cgc gga 1555 Val Cys Ala Val Ala Ala Ala Leu Ile Ser Ser Tyr Leu Phe Arg Gly 480 aat ccg aag gga gcc aat aat gcg cac tagtaaaaaa gagatgattc 1602 Asn Pro Lys Gly Ala Asn Asn Ala His 490 1605 tgc <210> 232 <211> 494 <212> PRT <213> Corynebacterium glutamicum <400> 232 Met Thr Ser Glu Thr Leu Gln Ala Gln Ala Pro Thr Lys Thr Gln Arg Trp Ala Phe Leu Ala Val Ile Ser Gly Gly Leu Phe Leu Ile Gly Val Asp Asn Ser Ile Leu Tyr Thr Ala Leu Pro Leu Leu Arg Glu Gln Leu Ala Ala Ser Glu Thr Gln Ala Leu Trp Ile Ile Asn Ala Tyr Pro Leu Leu Met Ala Gly Leu Arg Leu Gly Ala Gly Thr Leu Gly Asp Lys Asn

Gly His Arg Arg Met Phe Leu Met Gly Leu Ser Ile Phe Gly Ile Ala

Ser Leu Gly Ala Ala Phe Ala Pro Thr Ala Trp Ala Leu Val Ala Ala 100 105 110 Arg Ala Phe Leu Gly Ile-Gly Ala Ala Thr Met Met Pro Ala Thr Leu 115 120 125

- Ala Leu Ile Arg Ile Thr Phe Glu Asp Glu Arg Glu Arg Asn Thr Ala 130 135 140
- Ile Gly Ile Trp Gly Ser Val Ala Ile Leu Gly Ala Ala Ala Gly Pro 145 150 155 160
- Ile Ile Gly Gly Ala Leu Leu Glu Phe Phe Trp Trp Gly Ser Val Phe 165 170 175
- Leu Ile Asn Val Pro Val Ala Val Ile Ala Leu Ile Ala Thr Leu Phe 180 185 190
- Val Ala Pro Ala Asn Ile Ala Asn Pro Ser Lys His Trp Asp Phe Leu 195 200 205
- Ser Ser Phe Tyr Ala Leu Leu Thr Leu Ala Gly Leu Ile Ile Thr Ile 210 215 220
- Lys Glu Ser Val Asn Thr Ala Arg His Met Pro Leu Leu Gly Ala 225 230 235 240
- Val Ile Met Leu Ile Ile Gly Ala Val Leu Phe Ser Ser Arg Gln Lys 245 250 255
- Lys Ile Glu Glu Pro Leu Leu Asp Leu Ser Leu Phe Arg Asn Arg Leu 260 265 270
- Phe Leu Gly Gly Val Val Ala Ala Gly Met Ala Met Phe Thr Val Ser 275 280 285
- Gly Leu Glu Met Thr Thr Ser Gln Arg Phe Gln Leu Ser Val Gly Phe 290 295 300
- Thr Pro Leu Glu Ala Gly Leu Leu Met Ile Pro Ala Ala Leu Gly Ser 305 310 315 320
- Phe Pro Met Ser Ile Ile Gly Gly Ala Asn Leu His Arg Trp Gly Phe 325 330 335
- Lys Pro Leu Ile Ser Gly Gly Phe Ala Ala Thr Ala Val Gly Ile Ala 340 345 350
- Leu Cys Ile Trp Gly Ala Thr His Thr Asp Gly Leu Pro Phe Phe Ile 355 360 365
- Ala Gly Leu Phe Phe Met Gly Ala Gly Ala Gly Ser Val Met Ser Val 370 380
- Ser Ser Thr Ala Ile Ile Gly Ser Ala Pro Val Arg Lys Ala Gly Met 385 390 395 400
- Ala Ser Ser Ile Glu Glu Val Ser Tyr Glu Phe Gly Thr Leu Leu Ser 405 410 415

Val Ala Ile Leu Gly Ser Leu Phe Pro Phe Phe Tyr Ser Leu His Ala 420 425 430

Pro Ala Glu Val Ala Asp Asn Phe Ser Ala Gly Val His His Ala Ile 435 440 445

Asp Gly Asp Ala Ala Arg Ala Ser Leu Asp Thr Ala Tyr Ile Asn Val 450 455 460

Leu Ile Ile Ala Leu Val Cys Ala Val Ala Ala Ala Leu Ile Ser Ser 465 470 475 480

Tyr Leu Phe Arg Gly Asn Pro Lys Gly Ala Asn Asn Ala His
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aaa gtt ttg atc aac acc atg atc tcc aac gtc acc act gga ttt ctg 163 Lys Val Leu Ile Asn Thr Met Ile Ser Asn Val Thr Thr Gly Phe Leu 10 15 20

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ctg acc ggc atc gtc agt gga att tac atg ggt ttg atc gcc gtt tgt 259
Leu Thr Gly Ile Val Ser Gly Ile Tyr Met Gly Leu Ile Ala Val Cys
40 45 50

tcc atc ttt ttc gga acc gtt gtt gat cac aat cgc aag aag tcc gtc 307 Ser Ile Phe Phe Gly Thr Val Val Asp His Asn Arg Lys Lys Ser Val 55 60 65

atg ctg ttt tcc agc gtc acc aca ctc gtg ttt tat tgt ctc agt gcc 355
Met Leu Phe Ser Ser Val Thr Thr Leu Val Phe Tyr Cys Leu Ser Ala
70 75 80 85

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tgg tgg ctc tac atc ctg ggc att ttc atc ttc atg gct atc acc cca

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gct gcc gaa gcc Ala Ala Glu Ala 345	gca gaa c Ala Glu G	aa acc atc ln Thr Ile 350	Leu Gln	Arg val	gtc cca Val Pro 355	ttc 1171 Phe
cgc caa caa ggc Arg Gln Gln Gly 360	cgc gta to	tt gga cta he Gly Leu 365	gcc atg Ala Met	gca gtg Ala Val 370	gaa atg Glu Met	gca 1219 Ala
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atc ctc ggc gag Ile Leu Gly Glu	ggt aaa ge Gly Lys A 410	ct cgc ggc la Arg Gly	atg gca Met Ala 415	ctg atg Leu Met	ttc ctc Phe Leu 420	gca 1363 Ala
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tcc tac cgg aaa Ser Tyr Arg Lys 440	ctc agc ca Leu Ser G	ag tac tac ln Tyr Tyr 445	gcc acc Ala Thr	acc agc Thr Ser 450	caa gac Gln Asp	att 1459 Ile
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		25			30	
20 Thr Gly Asn Val	Ala Leu Th	25 nr Gly Ile 40	Val Ser	Gly Ile 45	30 Tyr Met	Gly

Tyr Cys Leu Ser Ala Leu Val Trp Val Phe Trp Leu Glu Glu Asp Gly 85 90 95

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- Leu Ser Ile Gly Asn Thr Ala Leu Trp Val Phe Val Ser Phe Ile Leu 100 105 110
- Ile Gly Ser Ile Val Glu His Met Arg Asn Ile Ala Leu Ser Thr Val 115 120 125
- Val Thr Leu Leu Val Pro Glu Ala Glu Arg Asp Lys Ala Asn Gly Leu 130 135 140
- Val Gly Ala Val Gln Gly Val Gly Phe Leu Val Thr Ser Val Ile Ala 145 150 155 160
- Gly Ser Ala Ile Gly Phe Leu Gly Met Glu Ile Thr Leu Trp Ile Cys 165 170 175
- Leu Gly Leu Ser Leu Val Ala Leu Leu His Leu Leu Pro Ile Arg Val 180 185 190
- Asp Glu Pro Glu Ile Ile Thr Gln Glu Asp Ala Gln Pro Thr Val Ser 195 200 205
- Asp Asp Ser Val Pro Thr Pro Thr Ser Asp Leu Ala Ile Val Ser Lys 210 225
- Gly Ile Asp Leu Lys Gly Ser Met Lys Ile Ile Leu Ser Val Pro Gly 225 230 235 240
- Leu Leu Ala Leu Val Leu Phe Ala Ser Phe Asn Asn Leu Ile Gly Gly 245 250 255
- Val Tyr Ser Ala Leu Met Asp Pro Tyr Gly Leu Glu Leu Phe Ser Pro 260 265 270
- Gln Leu Trp Gly Leu Leu Gly Leu Thr Ser Leu Gly Phe Ile Val 275 280 285
- Gly Gly Ala Val Ile Ser Lys Thr Gly Leu Gly Lys Asn' Pro Val Arg 290 295 300
- Thr Leu Leu Leu Val Asn Val Gly Val Ala Phe Val Gly Met Leu Phe 305 310 315 320
- Ala Ile Arg Glu Trp Trp Trp Leu Tyr Ile Leu Gly Ile Phe Ile Phe 325 330 335
- Met Ala Ile Thr Pro Ala Ala Glu Ala Ala Glu Gln Thr Ile Leu Gln 340 345 350
- Arg Val Val Pro Phe Arg Gln Gln Gly Arg Val Phe Gly Leu Ala Met 355 360 365
- Ala Val Glu Met Ala Ala Asn Pro Leu Ser Thr Val Ile Val Ala Ile 370 375 380

Leu Ala Glu Ala Tyr Leu Ile Pro Trp Met Ala Gly Pro Gly Ala Asp 390 . 385 Thr Ile Trp Gly Val Ile Leu Gly Glu Gly Lys Ala Arg Gly Met Ala 415 Leu Met Phe Leu Ala Ser Gly Ala Ile Met Leu Val Val Leu Leu 420 Ala Phe Met Ser Arg Ser Tyr Arg Lys Leu Ser Gln Tyr Tyr Ala Thr Thr Ser Gln Asp Ile Ala Gly Ala Ala Glu Lys 455 450 <210> 235 <211> 1521 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (101)..(1498) <223> RXA00062 <400> 235 cttcaacata ggcgttgggg ctgactttta aacaggtacc agtagtaccg gcataagcga 60 tcactgttgc gttttcttgc tgccatcaaa aattagtcac atg att tta agc atc Met Ile Leu Ser Ile 1 gtc ctt ttg ggc tac ttc atg att ctg ctt gac acc tcc atc gtc att 163 Val Leu Leu Gly Tyr Phe Met Ile Leu Leu Asp Thr Ser Ile Val Ile 10 acg ggt cta cct gcc atc ggc agt gaa ctt ggc atc gat ccc gtg cac 211 Thr Gly Leu Pro Ala Ile Gly Ser Glu Leu Gly Ile Asp Pro Val His 25 ctg tca tgg gtg cag agt tcc tac aca tta gtc ttc ggc gca ctt ctt 259 Leu Ser Trp Val Gln Ser Ser Tyr Thr Leu Val Phe Gly Ala Leu Leu 40 ctg ctg gga gct cgt gcc ggt gat atc ttc ggc cga aag aaa gtg ctc 307 Leu Leu Gly Ala Arg Ala Gly Asp Ile Phe Gly Arg Lys Lys Val Leu 60 55 tac att ggt etc gcg ttg ttt gcg gct tca tcg ttg gca att gcg ett 355 Tyr Ile Gly Leu Ala Leu Phe Ala Ala Ser Ser Leu Ala Ile Ala Leu 75 70 tet eca aat get geg gte etc att gga gea ege gta gtt caa gge geg 403 Ser Pro Asn Ala Ala Val Leu Ile Gly Ala Arg Val Val Gln Gly Ala 100 95

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1123

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caa ggc ttc gct Gln Gly Phe Ala 360	ttc gga c Phe Gly E	cca atg Pro Met 365	aca go	ct ctg la Leu	gca gtt Ala Val 370	caa ggt Gln Gly	gca Ala	1219
ccg aag gac caa Pro Lys Asp Gln 375	Ser Gly A	380	Ser G.	th red	385	501 200		1267
caa atc ggc ggc Gln Ile Gly Gly 390	acc ttc of Thr Phe 0 395	ggt ttg Gly Leu	ggt g Gly V	tg ttc al Phe 400	tcc tcc Ser Ser	ttg gct Leu Ala	gtc Val 405	1315
gct gtc atc gga Ala Val Ile Gly	cat gat of His Asp A	gca aca Ala Thr	Ser G	ag atg lu Met 15	atc agc Ile Ser	gac cgc Asp Arg 420	gca Ala	1363
cac ttc gga ttc His Phe Gly Phe 425	Leu Leu	tcc acc Ser Thr	gtg a Val T 430	cg ctg hr Leu	acg ctg Thr Leu	gcc acc Ala Thr 435	atc Ile	1411
ttt gcg gtc aca Phe Ala Val Thr 440	ctg ctg a	aag cgc Lys Arg 445	HIS G	aa acc lu Thr	cga aag Arg Lys 450	agt agc Ser Ser	gag Glu	1459
cgc cca acc cag Arg Pro Thr Gln 455	Leu Val	gac gaa Asp Glu 460	aag g Lys A	ca gtt la Val	acc tct Thr Ser 465	tagtgcg	ctg	1508
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Ile Asp Pro Val	His Leu	Ser Trp	Val G	in Ser	Ser Tyr	Thr Lev	val	
Phe Gly Ala Leu 50	leu Leu	Leu Gly 55	Ala A	Arg Ala	Gly Asp 60	lle Phe	Gly	
Arg Lys Lys Val	Leu Tyr	Ile Gly	Leu A	Ala Leu	Phe Ala	Ala Ser	Ser	•

65					70					75				19"	80
Leu	Ala	Ile	Ala	Leu 85	Ser	Pro	Asn	Ala	Ala 90	Val	Leu	Ile	Gly	Ala 95	Arg
Val	Val	Gln	Gly 100	Ala	Gly	Ala	Ala	Ile 105	Ile	Ala	Pro	Ala	Thr 110	Leu	Ala
Leu	Ile	Thr 115	Glu	Phe	Phe	Pro	Glu 120	Gly	Pro	Ala	Arg	Leu 125	Arg	Ala	Thr
Ser	Ala 130	Tyr	Gly	Ala	Val	Ala 135	Gly	Ile	Gly	Val	Ala 140	Ala	Gly	Leu	Val
Ile 145	Gly	Gly	Val	Phe	Ala 150	Asp	Leu	Leu	Ser	Trp 155	Arg	Ile	Gly	Phe	Phe 160
Ile	Asn	Val	Pro	Ile 165	Ala	Ala	Val	Leu	Ala 170	Tyr	Ile	Val	His	Lys 175	Ala
Ile	Pro	Ala	Thr 180	Phe	Ser	Arg	Pro	Gly 185	Ser	Leu	Asp	Ile	Phe 190	Gly	Ala
Ile	Thr	Ser 195	Thr	Ala	Gly	Ile	Ala 200	Ala	Val	Leu	Tyr	Ala 205	Ile	Val	Arg
Ser	Ala 210	Asp	Tyr	Ser	Trp	Thr 215	Asp	Pro	Phe	Val	Leu 220	Ile	Ser	Leu	Val
Leu 225	Gly	Ile	Ala	Val	Phe 230	Ile	Trp	Phe	Leu	Arg 235	His	Glu	Ser	Ser	Ala 240
Lys	Glu	Pro	Leu	Leu 245	Pro	Leu	Gly	Leu	Phe 250	Lys	Asn	Arg	Arg	Arg 255	Asn
Thr	Ile	Leu	Ala 260	Ser	Arg	Phe	Leu	Leu 265	Val	Gly	Ser	Val	Met 270	Ser	Phe
Phe	Phe	Phe 275	Ala	Thr	Gln	Leu	Phe 280	Gln	Asp	Thr	Met	Gly 285	Met	Asn	Ala
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Ser 305	Ala	Ala	Met	Val	Pro 310	Arg	Leu	Ser	Arg	Ala 315	Gly	Val	Ser	Asp	Ser 320
Met	Leu	Thr	Val	Ile 325	Gly	Phe	Ala	Ile	Met 330	Val	Ile	Gly	Met	Ala 335	Gly
Leu	Ala	Phe	Val 340	Pro	Asn	Thr	Met	11e 345	Ala	Leu	Ile	Leu	Pro 350	Ile	Val
Leu	Val	Gly 355	Phe	Gly	Gln	Gly	Phe 360	Ala	Phe	Gly	Pro	Met 365	Thr	Ala	. Leu

Ala Val Gln Gly Ala Pro Lys Asp Gln Ser Gly Ala Val Ser Gly Leu

375 380 370 Val Asn Ser Leu His Gln Ile Gly Gly Thr Phe Gly Leu Gly Val Phe 390 Ser Ser Leu Ala Val Ala Val Ile Gly His Asp Ala Thr Ser Glu Met 410 405 Ile Ser Asp Arg Ala His Phe Gly Phe Leu Leu Ser Thr Val Thr Leu 425 Thr Leu Ala Thr Ile Phe Ala Val Thr Leu Leu Lys Arg His Glu Thr Arg Lys Ser Ser Glu Arg Pro Thr Gln Leu Val Asp Glu Lys Ala Val 455 Thr Ser <210> 237 <211> 1584 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (101)..(1561) <223> RXA00215 <400> 237 cagtgcaaac tgaccccgca tcctaaaccg cgccagattt ctacctcaaa gaattgaagg 60 cettttecag gegeeetegt gegtgaaaga ataacteaac gtg tet gac aaa aag Val Ser Asp Lys Lys cag gat cta aca tcc tcc gca gca ggt agt gct gca ccc caa acc aag 163 Gln Asp Leu Thr Ser Ser Ala Ala Gly Ser Ala Ala Pro Gln Thr Lys 211 gcc tac ccc gcc atg ccc ttg cct gaa aag caa gct tgg cca gct cta Ala Tyr Pro Ala Met Pro Leu Pro Glu Lys Gln Ala Trp Pro Ala Leu 259 att gcc ttg tgc att ggg ttt ttc atg atc ctg ttg gat caa acc atc Ile Ala Leu Cys Ile Gly Phe Phe Met Ile Leu Leu Asp Gln Thr Ile 45 307 gtg gcc gtc tct acc cca gcg tta cag gca gac atg ggc gcg tcc tac Val Ala Val Ser Thr Pro Ala Leu Gln Ala Asp Met Gly Ala Ser Tyr 355 aac gag gtc atc tgg gta acc tcg gtg tat ctc ctc act ttc gcg gtg Asn Glu Val Ile Trp Val Thr Ser Val Tyr Leu Leu Thr Phe Ala Val

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gtc Val	tat Tyr	gtc Val	gca Ala 105	ggc Gly	atg Met	gtt Val	atc Ile	ttc Phe 110	aca Thr	gtg Val	agc Ser	tct Ser	ttg Leu 115	gcc Ala	tgt Cys	451
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Arg 150	Ile	Phe	Ala	ttt Phe	Glu 155	Arg	Arg	GIĀ	ATA	160	Leu	чету	Val	ırp	165	595
Ser	Thr	Ala	Gly	ctt Leu 170	Ala	Ser	Leu	Ala	G1y 175	Pro	116	Leu	GTÀ	180	Vai	643
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Ile	Gly	Val 200	Ile	tcg Ser	Val	Ile	Ala 205	Val	Met	гÀа	Tyr	210	FLO	GIU	1116	739
Pro	Pro 215	Leu	Thr	cga Arg	Pro	Leu 220	Asp	Pro	Leu	Ser	225	vai	Leu	Ser	116	787
Val 230	Ala	Val	_Phe	ttc Phe	Leu 235	Val	Phe	Ala	Pne	240	GIU	GIŞ	Giu	GIY	245	835
Gly	Trp	Ala	Ala	Trp 250	Val	Trp	Ile	Met	255	vai	Ата	HIG	FIIE	260	ctc Leu	883
Phe	Ala	Trp	Phe 265	Ile	Tyr	GIn	Gin	270	Arg	Ala	GIU	БÃЗ	275	01	aac Asn	931
Asp	Pro	Leu 280	Val	Pro	Leu	Glu	11e 285	Phe	Lys	Pne	Arg	290	FILE	261	ctc Leu	979
ggc Gly	aat Asn 295	Ile	tgc Cys	atc Ile	atg Met	gcc Ala 300	atg Met	gga Gly	ttc Phe	acc Thr	gtg Val 305	gct Ala	ggt Gly	act Thr	cct Pro	1027

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tcc act atg Ser Thr Met	cgc gae Arg Asi 41	Leu	cca Pro	cac His	aag Lys	ttc Phe 415	atg Met	gga Gly	gcg Ala	ggc Gly	tct Ser 420	ggc Gly	1363
gtg ttc aat Val Phe Asn	aca ace Thr Th: 425	c ege	caa Gln	tta Leu	ggt Gly 430	tca Ser	gtc Val	atc Ile	ggc Gly	gcc Ala 435	gct Ala	gcc Ala	1411
atc ggc gcg Ile Gly Ala 440	Val Me	g cag Gln	att Ile	cga Arg 445	ctg Leu	gca Ala	gca Ala	ggc Gly	gat Asp 450	gag Glu	ggc Gly	gca Ala	1459
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PCT/IB00/00922

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gca ctg tcc a Ala Leu Ser T	cc gtc gat gag hr Val Asp Glu 330	ttc gcc aac Phe Ala Asn 335	gtg tgg ttc atc Val Trp Phe Ile	atc ggc 1123 Ile Gly 340
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Ala Val Met I 390	le Ala Val Tyr 395	Ser Thr Val	agc aac aac gcg Ser Asn Asn Ala 400	405
Asp Gly Ala T	hr Gln Gln Thr 410	Ala Leu Ala 415	gac ggc gcc aac Asp Gly Ala Asn	420
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Phe	Met	Leu 35	Thr	Met	Ala	Val	Val 40	Leu	Pro	Ala	Thr	Gly 45	Trp	Met	Leu
Glu	Arg 50	Phe	Thr	Thr	Arg	Ser 55	Val	Phe	Ile	Phe	Ala 60	Thr	Val	Val	Phe
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			100					105					110		Gly
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_	130					135					140				Ala
145					150					155					Gly 160
				165					170					1/5	Asp
			180					185					190		Tyr
		195					200					205			Leu
	210					215					220				Arg
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Leu				245					250					255	
			260					265					270		Gln
		275					280					285			Pro
Gly	Gly 290		Leu	Glu	Gly	Val 295	Leu	Ser	Pro	Phe	Val 300	Gly	Arg	Ile	Tyr

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Gly 385	Ala	Ala	Gly	Thr	Ala 390	Val	Met	Ile	Ala	Val 395	Tyr	Ser	Thr	Val	Ser 400	
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Gly	Ala	Asn	Ser 420	Ala	Phe	Phe	Ala	Ser 425	Ala	Суз	Val	Ala	Val 430	Phe	Ala	
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Yal Leu Ser Pro Phe Val Gly Arg Ile Tyr Asp Arg His Gly Pro

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Ala Leu Ser Thr Val Asp

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Glu Arg Phe Thr Thr Arg Ser Val Phe Ile Phe Ala Thr Val Val Phe 50 55 60

Leu Ile Gly Thr Val Thr Ala Ala Leu Ser Pro Thr Phe Ala Ile Met 65 70 75 80

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Leu Leu Met Thr Val Ala Met Thr Val Val Pro Pro Glu Arg Arg Gly
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Gly Pro Ser Val Ala Gly Phe Val Leu Ser Leu Ser Ser Trp His Ala 130 135 140

Ile Phe Trp Val Met Val Pro Leu Val Phe Val Ala Ser Leu Ile Gly 145 150 155 160

Thr Leu Arg Leu Thr Asn Val Ser Glu Pro Lys Lys Thr Pro Leu Asp 165 170 175

Val Ile Ser Phe Leu Ile Ser Ala Val Ala Phe Gly Gly Leu Val Tyr 180 185 190

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пэр	Thr	Ser	Trp 20	Phe	Ser	Ser	Ala	Leu 25	Ala	Leu	Leu	Phe	Thr 30	Pro	Leu	
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Ser Ala Ile Leu Asn Thr Leu Gln Gln Leu Ala Gly Ala Ala Gly Thr
50 60

Ala Val Met Ile Ala Val Tyr Ser Thr Val Ser Asn Asn Ala Leu Ile 65 70 75 80

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205

195 200

Glu Trp Gly Trp Arg Ser Ala Leu Thr Ile Gly Leu Phe Val Ala Ala 210 215 220

Leu Val Ile Leu Val Gly Trp Gly Trp Phe Glu Thr Arg Gln Lys Ser 225 230 235 240

Pro Leu Ile Asp Leu Arg Thr Thr Ile Arg Ala Thr Val Leu Met Thr 245 250 255

Asn Ile Ala Ser Ile Leu Ile Gly Phe Thr Met Tyr Gly Met Asn Leu 260 265 270

Ile Leu Pro Gln Val Met Gln Leu Pro Val Ile Leu Gly Tyr Gly Leu 275 280 285

Gly Gln Ser Met Leu Gln Met Gly Ile Trp Leu Ile Pro Met Gly Leu 290 295 300

Gly Met Met Leu Ile Ser Asn Ala Gly Ala Ala Ile Ser Ala Ala His 305 310 315

Gly Pro Arg Val Thr Leu Thr Ile Ala Gly Val Val Ile Ala Val Gly
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Tyr Ala Leu Thr Ala Thr Val Leu Phe Thr Ile Gly Asn Arg Thr Pro 340 345 350

Gly Gly Asp Ala Asp Asn Ala Leu Ile Leu Thr Thr Leu Val Leu Phe 355 360 365

Ser Val Cys Ser Leu Val Val Gly Ile Gly Ile Gly Leu Ala Phe Gly 370 375 380

Ser Met Pro Ala Leu Ile Met Gly Ala Val Pro Ala Thr Glu Lys Ala 385 390 395 400

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Ser Ser Ala Val Ile Gly Ala Val Leu Ala Gly Met Met Ser Gly Gly
420 425 430

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PCT/IB00/00922 WO 01/00804

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Gln Asn Met Thr Thr Leu Ile Val Ala Arg Ala Leu Gln Gly Ile Ala

ggt ggt ggc ttg atg att ctt tct cag gca att acc gct gat gtc acc

Gly Gly Gly Leu Met Ile Leu Ser Gln Ala Ile Thr Ala Asp Val Thr

ace gee egt gag egt gea aag tac atg ggc ate atg ggt tee gtt tte

Thr Ala Arg Glu Arg Ala Lys Tyr Met Gly Ile Met Gly Ser Val Phe

155

150

160

175

595

643

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					gtt Val 235											835
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gct Ala	gcg Ala	ata Ile 280	gtg Val	ttc Phe	gtt Val	ttc Phe	gtc Val 285	gaa Glu	aag Lys	cgt Arg	gct Ala	gtt Val 290	gac Asp	cca Pro	ctg Leu	979
					ttc Phe											1027
					ggc Gly 315											1075
cct Pro	acc Thr	tac Tyr	ctg Leu	cag Gln 330	atg Met	gtt Val	cat His	ggt Gly	ctg Leu 335	aac Asn	cca Pro	acg Thr	caa Gln	gct Ala 340	ggt Gly	1123
					atg Met											1171
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	V	VO 01	/00 8 04	ı												PCT/IB00/009
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Thr	Ala	Asp	Val	Thr 165	Thr	Ala	Arg	Glu	Arg 170	Ala	Lys	Tyr	Met	Gly 175	Ile
Met	Gly	Ser	Val 180	Phe	Gly	Leu	Ser	Ser 185	Ile	Leu	Gly	Pro	Leu 190	Leu	Gly
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Ile	Phe	Met	Ala	Ile 245	Ala	Thr	Thr	Ala	Phe 250	Val	Leu	Ala	Val	Thr 255	Trp
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		275					Ile 280					285			
	290	_				295	Met				300				
Val 305	Leu	Thr	Ala	Val	Ala 310	Gly	Ile	Gly	Val	Gly 315	Leu	Phe	Met	Met	Gly 320
Thr	Ile	Ala	Tyr	Met 325	Pro	Thr	Tyr	Leu	Gln 330	Met	Val	His	Gly	Leu 335	Asn
Pro	Thr	Gln	Ala 340	Gly	Leu	Met	Leu	Ile 345	Pro	Met	Met	Ile	Gly 350	Leu	Ile
Gly	Thr	Ser 355	Thr	Vạl	Val	Gly	Asn 360	Ile	Val	Ser	Lys	Thr 365	Gly	Lys	Tyr

Lys Trp Tyr Pro Phe Ile Gly Met Leu Ile Met Val Leu Ala Leu Val 375 370 Leu Leu Ser Thr Leu Thr Pro Ser Ala Ser Leu Ala Leu Ile Gly Leu 395 Tyr Phe Phe Val Phe Gly Phe Gly Leu Gly Cys Ala Met Gln Ile Leu 410 Val Leu Ile Val Gln Asn Ser Phe Pro Ile Thr Met Val Gly Thr Ala 420 Thr Gly Ser Asn Asn Phe Phe Arg Gln Ile Gly Gly Ala Val Gly Ser Ala Leu Ile Gly Gly Leu Phe Ile Ser Asn Leu Ser Asp Arg Phe Thr Glu Asn Val Pro Ala Ala Val Ala Ser Met Gly Glu Glu Gly Ala Gln Tyr Ala Ser Ala Met Ser Asp Phe Ser Gly Ala Ser Asn Leu Thr Pro His Leu Val Glu Ser Leu Pro Gln Ala Leu Arg Glu Ala Ile Gln Leu Ser Tyr Asn Asp Ala Leu Thr Pro Ile Phe Leu Ala Leu Thr Pro Ile Ala Val Val Ala Ala Ile Leu Leu Phe Phe Ile Arg Glu Asp His Leu 535 Lys Glu Thr His Glu 545 <210> 249 <211> 841 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (101)..(841) <223> FRXA01314 <400> 249 gtgaatggca cgacatgcca caaggcacgc aagctgattt ccaagcctgc tgtcgcaaag 60 caattaaaaa tacttttctt cttagaggtg gattttcaga atg aca tca cag gtc Met Thr Ser Gln Val aag ccg gac gac gaa cgt ccg gta aca aca att tca aaa agt ggt gca Lys Pro Asp Asp Glu Arg Pro Val Thr Thr Ile Ser Lys Ser Gly Ala 20 15

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35 40 45

Phe Ile Ile Ala Ala Leu Met Leu Ala Met Leu Leu Ser Ser Leu Gly 50 55 60

Gin Thr Ile Phe Gly Ser Ala Leu Pro Thr Ile Val Gly Glu Leu Gly 65 70 75 80

Gly Val Asn His Met Thr Trp Val Ile Thr Ala Phe Leu Leu Gly Gln 85 90 95

Thr Ile Ser Leu Pro Ile Phe Gly Lys Leu Gly Asp Gln Phe Gly Arg
100 105 110

Lys Tyr Leu Phe Met Phe Ala Ile Ala Leu Phe Val Val Gly Ser Ile 115 120 125

Ile Gly Ala Leu Ala Gln Asn Met Thr Thr Leu Ile Val Ala Arg Ala 130 135 140

Leu Gln Gly Ile Ala Gly Gly Gly Leu Met Ile Leu Ser Gln Ala Ile 145 150 155 160

Thr Ala Asp Val Thr Thr Ala Arg Glu Arg Ala Lys Tyr Met Gly Ile 165 170 175

Met Gly Ser Val Phe Gly Leu Ser Ser Ile Leu Gly Pro Leu Leu Gly 180 185 190

Gly Trp Phe Thr Asp Gly Pro Gly Trp Arg Trp Gly Leu Trp Leu Asn 195 200 205

Val Pro Ile Gly Ile Ile Ala Leu Val Ala Ile Ala Val Leu Leu Lys 210 215 220

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acg caa gct ggt ctg atg ctg atc cca atg atg atc ggc ctg att ggt Thr Gln Ala Gly Leu Met Leu Ile Pro Met Met Ile Gly Leu Ile Gly 50 55 60	192 7
aca tcc act gtg gtg ggc aac atc gtg tcc aag act ggc aag tac aag Thr Ser Thr Val Val Gly Asn Ile Val Ser Lys Thr Gly Lys Tyr Lys 65 70 75 80	3
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gta gtc gcc gcg atc ctc ctc ttt ttc atc cgt gaa gat cac c Val Val Ala Ala Ile Leu Leu Phe Phe Ile Arg Glu Asp His I 245 250 2	etc aag 768 Leu Lys 255
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atc Ile	atc Ile	att Ile	gga Gly 265	ctg Leu	atc Ile	atc Ile	acc Thr	acc Thr 270	atc Ile	gtt Val	gcc Ala	gct Ala	gca Ala 275	ctg Leu	ctg Leu	931
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tcc Ser	aac Asn	aca Thr 360	gga Gly	aag Lys	tac Tyr	aaa Lys	ctc Leu 365	ttc Phe	cca Pro	cca Pro	atc Ile	ggc Gly 370	atg Met	gtg Val	gtt Val	1219
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Val Met Met Pro Leu Ile Gly Ile Ala Leu Leu Leu Leu Phe Ile
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Ala Leu Met Val Ala Met Met Met Ala Ser Leu Asp Gln Met Ile Phe 50 55 60

Gly Thr Ala Leu Pro Thr Ile Val Gly Glu Leu Gly Gly Val Asp His 65 70 75 80

Met Met Trp Val Ile Thr Ala Tyr Leu Leu Ala Glu Thr Ile Met Leu 85 90 95

Pro Ile Tyr Gly Lys Leu Gly Asp Leu Val Gly Arg Lys Gly Leu Phe 100 105 110

Ile Gly Ala Leu Gly Ile Phe Leu Ile Gly Ser Val Ile Gly Gly Leu 115 120 125

Ala Gly Asn Met Thr Trp Leu Ile Val Gly Arg Ala Val Gln Gly Ile 130 135 140

Gly Gly Gly Leu Met Ile Leu Ser Gln Ala Ile Ile Ala Asp Val 145 150 155 160

Val Pro Ala Arg Glu Arg Gly Arg Tyr Met Gly Val Met Gly Gly Val 165 170 175

Phe Gly Leu Ser Ala Val Leu Gly Pro Leu Leu Gly Gly Trp Phe Thr 180 185 190

Glu Gly Pro Gly Trp Arg Trp Ala Phe Trp Met Asn Ile Pro Leu Gly 195 200 205

Ile Ile Ala Ile Gly Val Ala Ile Tyr Phe Leu Asp Ile Pro Lys Lys Ser Val Lys Phe Arg Trp Asp Tyr Leu Gly Thr Phe Phe Met Ile Val 235 Ala Ala Thr Ser Leu Ile Leu Phe Thr Thr Trp Gly Gly Ser Gln Tyr 250 Glu Trp Ser Asp Pro Ile Ile Ile Gly Leu Ile Ile Thr Thr Ile Val Ala Ala Leu Leu Val Val Val Glu Leu Arg Ala Lys Asp Pro Leu Val Pro Met Ser Phe Phe Gln Asn Arg Asn Phe Thr Leu Thr Thr Ile Ala Gly Leu Ile Leu Gly Ile Ala Met Phe Gly Ile Ile Gly Tyr Leu Pro Thr Tyr Leu Gln Met Val His Gly Ile Asn Ala Thr Glu Ala Gly Tyr Met Leu Ile Pro Met Met Val Gly Met Met Gly Thr Ser Ile Trp Thr Gly Ile Arg Ile Ser Asn Thr Gly Lys Tyr Lys Leu Phe Pro Pro Ile Gly Met Val Val Thr Phe Val Ala Leu Ile Phe Phe Ala Arg Met 380 Glu Val Ser Thr Thr Leu Trp Gln Ile Gly Ile Tyr Leu Phe Val Leu Gly Val Gly Leu Gly Leu Ala Met Gln Val Leu Val Leu Ile Val Gln Asn Thr Leu Pro Thr Ala Val Val Gly Ser Ala Thr Ala Val Asn Asn Phe Phe Arg Gln Ile Gly Ser Ser Leu Gly Ser Ala Leu Val Gly Gly 440 Met Phe Val Gly Asn Leu Gly Thr Leu Met Glu Glu Arg Met Pro Ala Ala Met Ala Gln Leu Ser Pro Glu Glu Gln Ala Ala Met Ala Ala Gln 465 Gly Gly Leu Asp Ser Asn Glu Leu Thr Pro Ala Ile Val Asn Gln Leu 490 Pro Thr Ala Leu His Asp Ala Phe Ala Gly Ser Tyr Asn Asp Ala Leu

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atg atg gcc tcc ctt gac cag atg att ttc ggc aca gcc ctg cca Met Met Met Ala Ser Leu Asp Gln Met Ile Phe Gly Thr Ala Leu Pro 55 60 65	307
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acc gca tac cta ctt gcc gaa acc atc atg ctg ccg atc tac gga aag Thr Ala Tyr Leu Leu Ala Glu Thr Ile Met Leu Pro Ile Tyr Gly Lys 90 95 100	403
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	atg Met	tgg Trp 425	gct Ala	ggc Gly	gtg Val	atc Ile	atc Ile 430	ttg Leu	gtc Val	cta Leu	gcc Ala	ttc Phe 435	ctc Leu	tgc Cys	tcc Ser	ctg Leu	1409
	ctg Leu 440	atc Ile	cca Pro	cgc Arg	cca Pro	gaa Glu 445	tca Ser	atc Ile	acc Thr	gat Asp	aca Thr 450	gtg Val	gca Ala	gcc Ala	aaa Lys	gtc Val 455	1457
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1510

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Ser Thr Ala Glu Glu Thr Pro Lys Met Asp Trp Leu Gly Val Leu Pro

Leu Ala Val Ser Ile Gly Ser Leu Leu Met Ala Phe Asn Glu Ala Gly

Lys Leu Gly Ala Ala Asn Trp Ile Leu Val Val Leu Phe Ile Ile

Gly Ile Ala Gly Val Ile Phe Phe Tyr Asn Ile Glu Lys Arg Val Lys

His Pro Leu Val Ser Val Glu Tyr Leu Gly Gln Arg Arg Thr Trp Ala 250 245

Leu Leu Ser Thr Leu Leu Thr Met Thr Gly Val Phe Ala Val Met Asn Gly Leu Leu Pro Asn Leu Ala Gln Asp Ala Ala Asn Gly Ala Gly 280 Met Ser Ala Ser Val Val Ser Trp Trp Thr Leu Thr Pro Tyr Ala Leu Ala Gly Leu Val Phe Gly Pro Ile Ala Gly Ile Leu Ala Gly Lys Phe Gly Tyr Lys Ile Val Leu Gln Ile Gly Ile Ala Ala Thr Ile Ile Gly Val Ala Gly Ala Thr Phe Leu Val Gly Ser Thr Ser His Leu Ala Tyr Leu Gly Ile Ser Ile Phe Val Gly Ile Thr Tyr Ala Gly Ile Ala Asn Ile Met Leu Asn Gly Leu Gly Ile Val Leu Ser Pro Ala Asn Asn Gln Gly Tyr Leu Pro Gly Met Asn Ala Gly Ala Phe Asn Leu Gly Ala Gly 390 Ile Ser Phe Ala Ile Leu Phe Ala Val Ser Thr Ala Phe Ser Asp Asn Gly Gly Gly Tyr Ala Ala Gly Met Trp Ala Gly Val Ile Ile Leu Val Leu Ala Phe Leu Cys Ser Leu Leu Ile Pro Arg Pro Glu Ser Ile Thr Asp Thr Val Ala Ala Lys Val Gln Ala Glu Glu Ala Ala Gln Ala Ala 455 450 Ser 465 <210> 259 <211> 1470 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (101)..(1447) <223> RXA02087 aatcggattc atgctgtgtg gtgtgatcag tttgctggct gcggtcgcat ggatcttcgg 60

WO 01/00804	PCT/IB00/00922

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gag too agg gog tgg aaa got otg ggo got tta	agt gtt ggg ctg ttt 163
Glu Ser Arg Ala Trp Lys Ala Leu Gly Ala Leu	Ser Val Gly Leu Phe
10 15	20
ctc aca ctg ctt gac caa tcg ttg gtg gct gtc	gcg ctg cca aag att 211
Leu Thr Leu Leu Asp Gln Ser Leu Val Ala Val	Ala Leu Pro Lys Ile
25 30	35
caa gag gat ttg ggt gcg agc ctg aac caa gcg	gtg tgg gtg tca gcg 259
Gln Glu Asp Leu Gly Ala Ser Leu Asn Gln Ala	Val Trp Val Ser Ala
40 45	50
gtt tat ttg ctc act ttt gcg gtg cca ctg ttg	att act ggg cgc ttg 307
Val Tyr Leu Leu Thr Phe Ala Val Pro Leu Leu	Ile Thr Gly Arg Leu
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Gly Asp Arg Tyr Gly Gln Arg Asn Ile Tyr Leu	Ala Gly Met Ala Val
70 75 80	85
ttt acc ctc gcg gcg ttg gcc tgt gta ttt gca	cca agc atc gaa tgg 403
Phe Thr Leu Ala Ala Leu Ala Cys Val Phe Ala	Pro Ser Ile Glu Trp
90 95	100
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Leu Ile Ala Ala Arg Ala Val Gln Gly Leu Gly	Gly Ser Leu Leu Asn
105 110	115
ccg cag ccc ctg agc atc att cac aag att ttc	gcg cat gat cgt agg 499
Pro Gln Pro Leu Ser Ile Ile His Lys Ile Phe	Ala His Asp Arg Arg
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Gly Ala Ala Thr Gly Val Trp Ser Ala Val Ala	Ser Ser Ala Gly Leu
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Phe Gly Pro Val Ile Gly Gly Val Leu Val Gly	Trp Ile Ser Trp Arg
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Ala Val Phe Leu Val Tyr Val Pro Leu Gly Leu	Ile Ser Leu Phe Met
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Val Ala Arg Tyr Val Pro Lys Leu Pro Thr Gly	Thr Ser Lys Ile Asp
185 190	195
tgg ctc tcg ggt gcg gtc tca ctt gtt gct gta	ctt ggt gtg gtt ctt 739
Trp Leu Ser Gly Ala Val Ser Leu Val Ala Val	Leu Gly Val Val Leu
200 205	210
gcc ttg cag cag ggg cca gaa ctt ggg tgg gga	aca ctg att tgg gtg 787

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aac Asn	ttc Phe	gcg Ala	atc Ile 265	ggt Gly	gca Ala	ttt Phe	tcg Ser	atc Ile 270	ttc Phe	agc Ser	ctg Leu	ggc Gly	ttt Phe 275	acg Thr	gtg Val	931
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cca Pro	gga Gly	atg Met	atc Ile	tcc Ser 330	aag Lys	atc Ile	gga Gly	ttc Phe	ggc Gly 335	gcg Ala	ctg Leu	att Ile	ttc Phe	tcg Ser 340	atg Met	1123
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ctc Leu	atc Ile	ccg Pro 360	att Ile	att Ile	ttg Leu	ttc Phe	ggt Gly 365	agc Ser	tcc Ser	aac Asn	gcg Ala	atg Met 370	agt Ser	ttt Phe	gca Ala	1219
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Val Trp Val Ser Ala Val Tyr Leu Leu Thr Phe Ala Val Pro Leu Leu 50 55 60

Ile Thr Gly Arg Leu Gly Asp Arg Tyr Gly Gln Arg Asn Ile Tyr Leu 65 70 75 80

Ala Gly Met Ala Val Phe Thr Leu Ala Ala Leu Ala Cys Val Phe Ala 85 90 95

Pro Ser Ile Glu Trp Leu Ile Ala Ala Arg Ala Val Gln Gly Leu Gly 100 105 110

Gly Ser Leu Leu Asn Pro Gln Pro Leu Ser Ile Ile His Lys Ile Phe 115 120 125

Ala His Asp Arg Arg Gly Ala Ala Thr Gly Val Trp Ser Ala Val Ala 130 135 140

Ser Ser Ala Gly Leu Phe Gly Pro Val Ile Gly Gly Val Leu Val Gly 145 150 155 160

Trp Ile Ser Trp Arg Ala Val Phe Leu Val Tyr Val Pro Leu Gly Leu 165 170 175

Ile Ser Leu Phe Met Val Ala Arg Tyr Val Pro Lys Leu Pro Thr Gly 180 185 190

Thr Ser Lys Ile Asp Trp Leu Ser Gly Ala Val Ser Leu Val Ala Val 195 200 205

Leu Gly Val Val Leu Ala Leu Gln Gln Gly Pro Glu Leu Gly Trp Gly 210 215 220

Thr Leu Ile Trp Val Ser Leu Ala Val Gly Ile Ala Ala Ala Val Leu 225 230 235 240

Phe Ile Trp Met Gln Thr Arg Ser Lys Ala Pro Leu Met Pro Leu Arg

250 245

Ile Phe Lys Thr Arg Asn Phe Ala Ile Gly Ala Phe Ser Ile Phe Ser

Leu Gly Phe Thr Val Tyr Ser Val Asn Leu Pro Ile Met Leu Tyr Leu 280

Gln Thr Ala Gln Gly Met Ser Ser Gln Leu Ala Gly Leu Met Leu Val

Pro Met Gly Ile Ile Ser Val Val Met Ser Pro Val Ile Gly Arg Leu

Val Asp Arg Leu Ala Pro Gly Met Ile Ser Lys Ile Gly Phe Gly Ala 330

Leu Ile Phe Ser Met Ala Leu Met Ala Val Phe Met Ile Ala Asn Leu

Ser Pro Trp Trp Leu Leu Ile Pro Ile Ile Leu Phe Gly Ser Ser Asn

Ala Met Ser Phe Ala Pro Asn Ser Val Ile Ala Leu Arg Asp Val Pro

Gln Asp Leu Val Gly Ser Ala Ser Gly Phe Tyr Asn Thr Ser Arg Gln

Val Gly Ala Val Leu Gly Ala Ala Thr Leu Gly Ala Val Met Gln Ile

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Arg

<210> 261

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<223> RXA02088

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PCT/IB00/00922 WO 01/00804 5 1 ata gaa tta gag gct aaa cca aaa atc cca gag gag atc tgg gtg ctg 163 Ile Glu Leu Glu Ala Lys Pro Lys Ile Pro Glu Glu Ile Trp Val Leu gtt gtg gct gcg ttt att att gcg ctg ggc tat ggc ctg att gcg ccg 211 Val Val Ala Ala Phe Ile Ile Ala Leu Gly Tyr Gly Leu Ile Ala Pro att ttg cca cag ttt gtg gtc ggt ttt gat gta agt ttt gca gct gcc 259 Ile Leu Pro Gln Phe Val Val Gly Phe Asp Val Ser Phe Ala Ala Ala 45 agt gcg gtg gtg tcc atc ttt gcg ggc gcc cgg ttg ttg ttt gcg ccg 307 Ser Ala Val Val Ser Ile Phe Ala Gly Ala Arg Leu Leu Phe Ala Pro atg tcg ggg agt ttg atc gat aag atc ggt tcc cgt cgt gtg tat ctc 355 Met Ser Gly Ser Leu Ile Asp Lys Ile Gly Ser Arg Arg Val Tyr Leu act ggt tta ctc acc gtg gct atc acc acg ggg ctt gtt gcg ttg gcg 403 Thr Gly Leu Leu Thr Val Ala Ile Thr Thr Gly Leu Val Ala Leu Ala cag gaa tac tgg cag att ctg ctg ctt cgt ggc atc gca ggt att ggt Gln Glu Tyr Trp Gln Ile Leu Leu Leu Arg Gly Ile Ala Gly Ile Gly 105 tcc acc atg ttt acg gtc tct gcc atg ggc ctg atc gtg aag atg gcg 499 Ser Thr Met Phe Thr Val Ser Ala Met Gly Leu Ile Val Lys Met Ala 120 ccg gtg gag atc cgc ggg cgg tgt tcg tcg gta tat gcc agt tcg ttc 547 Pro Val Glu Ile Arg Gly Arg Cys Ser Ser Val Tyr Ala Ser Ser Phe 135 ctg ttt ggc aat att att ggc ccg gtt gtg ggt gct gcg atg tcc ggt 595 Leu Phe Gly Asn Ile Ile Gly Pro Val Val Gly Ala Ala Met Ser Gly 150 ttg ggc atg cgg tgg ccg ttc gcg att tat ggt gct tcc gtt ggc tta 643 Leu Gly Met Arg Trp Pro Phe Ala Ile Tyr Gly Ala Ser Val Gly Leu 170 gct gca ctt gtt gtg tgg tgg cgg atg ccg aaa acc aac gat tca ctt 691 Ala Ala Leu Val Val Trp Trp Arg Met Pro Lys Thr Asn Asp Ser Leu 190

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Arg Lys Ala Asp Ser Asn Ser Val Pro Ala Leu Arg Phe Ala Glu Ala

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225

739

787

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<211> 405 <212> PRT

<213> Corynebacterium glutamicum

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Ala Gly Leu Leu Asn Pro Ser Gln Gln Ala Val Leu Ala Asp Val Ile 330 Asp Ser Arg Pro Gly Gly Lys Val Leu Ala Asn Phe Gln Met Ala Gln Asp Phe Gly Ala Ile Val Gly Pro Ile Leu Val Gly Met Ile Ala Glu Gln Ala Gly Phe Gln Ile Gly Phe Met Leu Cys Gly Val Ile Ser Leu Leu Ala Ala Val Ala Trp Ile Phe Gly Arg Glu Thr Leu Pro Thr Ala 390 Lys Val Glu Gln Val <210> 263 <211> 1239 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (101)..(1216) <223> RXA00764 <400> 263 tactgcgtcg gatccgctga tgcttgcaga atcggacagt gatgggccgt ctgcgcctgc 60 acctgggacg actggattat taggggtgga attttcgctc atg aca ctc aag act Met Thr Leu Lys Thr 1 age gtt ttg gca cta ctc tta gat aac gtg cat gtt ctt ctg att gcg 163 Ser Val Leu Ala Leu Leu Leu Asp Asn Val His Val Leu Leu Ile Ala 10 aat cct gag tcg acc acg cag acg cag aaa ctt ttc cgt cgt gtg gtg 211 Asn Pro Glu Ser Thr Thr Gln Thr Gln Lys Leu Phe Arg Arg Val Val 259 cet geg ttg atg geg ett gat ggt gtg teg ett gaa geg agg ttt aeg Pro Ala Leu Met Ala Leu Asp Gly Val Ser Leu Glu Ala Arg Phe Thr cac tat gga ggc cat gcg gag gaa atg gtt gcg ggt ttg acg gtg gat 307 His Tyr Gly Gly His Ala Glu Glu Met Val Ala Gly Leu Thr Val Asp gat ttt gat gtg att atc ccc gcg ggt ggg gac ggc acc gtc aac gaa 355 Asp Phe Asp Val Ile Ile Pro Ala Gly Gly Asp Gly Thr Val Asn Glu gtg ata aat ggg tta ctt ggg tcg gcg gaa ggt gat ttt aga aac ctt 403

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	gct Ala	GJ Å dad	ttt Phe	ggt Gly	att Ile 170	gat Asp	gcg Ala	gat Asp	gtt Val	att Ile 175	gcc Ala	agg Arg	gtc Val	gaa Glu	cgg Arg 180	gcg Ala	643
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Leu Val Leu Leu Val Phe Arg Ser Ile Trp Val Pro Leu Ile Ala get etg gge tit gge tig tea git etg get ace tit ggt get ace gtg 211 Ala Leu Gly Phe Gly Leu Ser Val Leu Ala Thr Phe Gly Ala Thr Val geg atc ttc caa gaa ggt gct ttc ggc atc atc gac gat cct cag cca 259 Ala Ile Phe Gln Glu Gly Ala Phe Gly Ile Ile Asp Asp Pro Gln Pro 271 ctg ctg tgc ttc Leu Leu Cys Phe 55 <210> 266 <211> 57 <212> PRT <213> Corynebacterium glutamicum <400> 266 Leu Val Leu Ala Phe Leu Val Leu Leu Leu Val Phe Arg Ser Ile Trp Val Pro Leu Ile Ala Ala Leu Gly Phe Gly Leu Ser Val Leu Ala Thr 25 Phe Gly Ala Thr Val Ala Ile Phe Gln Glu Gly Ala Phe Gly Ile Ile Asp Asp Pro Gln Pro Leu Leu Cys Phe 50 <210> 267 <211> 1443 <212> DNA <213> Corynebacterium glutamicum <220> <221> CDS <222> (101)..(1420) <223> RXN01553 <400> 267 atgatgatgt cctcagcaag tccaagcgcc aagccatgct ggaaacaatt ctcgagctga 60 taccaagcca gacttaaatt tctaccttaa agtcttgagc atg act gtt cag gaa Met Thr Val Gln Glu ttc gac cgc gcg acc aaa ccc aca cca aaa ccc cca att gtt tct tgg 163 Phe Asp Arg Ala Thr Lys Pro Thr Pro Lys Pro Pro Ile Val Ser Trp 211 gcg ttt tgg gat tgg ggt tcc gcc tct ttc aac gcg gtc ctc gtg acc

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Ser Tyr Leu Thr 370	Arg Leu Ser 375	Pro Asp Gly Gln	Glu Gly Gln Leu 380	Phe
Gly Leu Tyr Ala 385	Thr Thr Gly 390	Arg Ala Val Ser 395	Trp Met Val Pro	Ser 400
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Tyr Arg Leu Arg Arg Thr Glu Ile Phe Trp Ala Thr Leu Leu Thr Val 50 55 60

Ala Val Gly Ile Met Ile Val Leu Gly Arg Pro Leu Pro Gly Asn Pro 65 70 75 80

His Pro Pro Leu Asp Arg Trp Ile Pro Val Leu Leu Val Gly Val Ala 85 90 95

Val Met Gly Gly Met Trp Leu Leu Ala Glu Tyr Val Leu Lys Lys Asp 100 105 110

Lys Ala Leu Ile Leu Gly Leu Val Thr Gly Ala Leu Phe Gly Tyr Val 115 120 125

Ala Val Met Ser Lys Ala Ala Val Asp Leu Phe Val His Gln Gly Ile 130 135 140

Thr Gly Leu Ile Leu Asn Trp Glu Gly Tyr Gly Leu Ile Leu Thr Ala 145 150 155 160

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Gln Lys Ser Leu Pro Ala Met Thr Ile Ala Glu Pro Ile Val Ala Phe 180 185 190

Ser Leu Gly Tyr Leu Val Leu Gly Glu Lys Phe Gln Val Val Asp Trp 195 200 205

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aat Asn	att Ile	gat Asp	acc Thr 425	act Thr	cag Gln	cgt Arg	cag Gln	tcg Ser 430	gct Ala	gat Asp	ttg Leu	atg Met	gca Ala 435	gag Glu	ggc Gly	1411

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gag Glu	gtc Val 455	aat Asn	gct Ala	gat Asp	tcc Ser	acc Thr 460	gca Ala	ttg Leu	cag Gln	cca Pro	ctg Leu 465	att Ile	gag Glu	gca Ala	cag Gln	1507
gag Glu 470	cct Pro	gaa Glu	gag Glu	ggc Gly	gag Glu 475	ttc Phe	gat Asp	cgg Arg	gag Glu	cag Gln 480	gcg Ala	gct Ala	cgt Arg	ttt Phe	gct Ala 485	1555
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ctc Leu	gtg Val	act Thr 520	cca Pro	tac Tyr	acc Thr	gga Gly	cct Pro 525	gcg Ala	gat Asp	aaa Lys	gag Glu	acc Thr 530	cct Pro	gag Glu	ttg Leu	1699
Met	His 535	Val	Leu	Arg	Ala	Gln 540	Glu	Ala	Gln	att Ile	G1u 545	Asp	Val	Thr	GIĀ	1747
Thr 550	Glu	Leu	Gly	Thr	Thr 555	Gly	Phe	Thr	Ala	gtt Val 560	GIn	Leu	Asp	11e	565	1795
Glu	Gln	Leu	Glu	Asp 570	Ala	Met	Pro	Val	Tyr 575	ctc Leu	Ala	vaı	Val	580	GTÀ	1843
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Ala	Thr 615	Val	Leu	Val	Trp	Gln 620	Glu	Gly	Phe	ggt Gly	G1y 625	Phe	Val	Asn	Thr	1987
Pro 630	Gly	Pro	Leu	Ile	Ser 635	Phe	Met	Pro	Ile	ttc Phe 640	Leu	Ile	Gly	Val	1nr 645	2035
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WO 01/	00804								`		PCT/IB00/00922
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gtg gtt aca Val Val Thr 695	gca gcg Ala Ala	gca ctg Ala Leu 700	atc atg Ile Met	att	Ala '	gtg Val 705	ttc Phe	gtg Val	gcg Ala	ttt Phe	2227
att gat cag Ile Asp Gln 710	ccg ttg Pro Leu	cca ttt Pro Phe 715	att aag Ile Lys	Ile	ttc (Phe (720	ggt Gly	ttc Phe	gcg Ala	ttg Leu	ggt Gly 725	2275
gcg ggc gtg Ala Gly Val	ttt ttc Phe Phe 730	Asp Ala	ttc ttc Phe Phe	att Ile 735	cgc (Arg	atg Met	ggt Gly	ctg Leu	gtc Val 740	ccc Pro	2323
gcg tcg atg Ala Ser Met	ttc ctg Phe Leu 745	atg ggc Met Gly	aag gcc Lys Ala 750	Thr	tgg ' Trp '	tgg Trp	atg Met	cct Pro 755	aag Lys	tgg Trp	2371
ctg gat cga Leu Asp Arg 760	att ctg Ile Leu	cca agt Pro Ser	ttg gac Leu Asp 765	att	gaa (Glu (ggc Gly	acc Thr 770	gca Ala	ctg Leu	gag Glu	2419
aag gaa tgg Lys Glu Trp 775	gag gag Glu Glu	aag cag Lys Gln 780	gct gca Ala Ala	cgt Arg	taga	cttg	ıgc a	ccta	atgto	ca	2469
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Pro Ser Ile 35	Asp Ala	Thr Val	Ser Leu 40	Val	Glu .	Asn	Phe 45	Pro	Asp	Gln	
Thr Asn Pro 50	Val Thr	Ala Ala 55	Gly Val	Asn	Val '	Val 60	Phe	Gln	Ser	Pro	
Glu Gly Thr 65	Thr Leu	Asp Asp 70	Pro Gln	Met	Met :	Thr	Ala	Met	Asp	Ala 80	

Val Val Asp Tyr Ile Glu Asp Asn Leu Pro Asp Phe Gly Gly Glu 85 90 95

Arg Phe Gly Asn Pro Val Glu Val Ser Pro Ala Leu Glu Glu Met Val Ile Glu Gln Met Thr Ser Met Gly Leu Pro Glu Glu Thr Ala Ala Lys 120 Asp Ala Ala Asn Leu Ala Val Leu Ser Glu Asp Lys Thr Ile Gly Tyr 135 Thr Ser Phe Asn Ile Asp Val Glu Ala Ala Glu Tyr Val Glu Gln Lys 155 His Arg Asp Val Ile Asn Glu Ala Met Gln Ile Gly Glu Asp Leu Gly 165 Val Arg Val Glu Ala Gly Gly Pro Ala Phe Gly Asp Pro Ile Gln Ile Glu Thr Thr Ser Glu Ile Ile Gly Ile Gly Ile Ala Phe Ile Val Leu Ile Phe Thr Phe Gly Ser Leu Ile Ala Ala Gly Leu Pro Leu Ile Thr Ala Val Ile Gly Val Gly Ile Gly Ala Leu Ala Ile Val Leu Ala Thr Ala Phe Thr Asp Leu Asn Asn Val Thr Pro Val Leu Ala Val Met Ile 250 Gly Leu Ala Val Gly Ile Asp Tyr Ala Leu Phe Ile Leu Ser Arg Tyr Arg Ala Glu Tyr Lys Arg Met Pro Arg Ala Asp Ala Ala Gly Met Ala 280 Val Gly Thr Ala Gly Ser Ala Val Val Phe Ala Gly Ala Thr Val Ile 295 Ile Ala Leu Val Ala Leu Ile Ile Ala Asp Ile Gly Phe Leu Thr Ala Met Gly Ile Ser Ala Ala Phe Thr Val Phe Val Ala Val Leu Ile Ala Leu Thr Phe Ile Pro Ala Leu Leu Gly Val Phe Gly Gly His Ala Phe Lys Gly Lys Ile Pro Gly Ile Gly Gly Asn Pro Thr Pro Lys Gln Thr 360 Trp Glu Gln Ala Leu Asn Arg Arg Ser Lys Gly Arg Ser Trp Val Lys Leu Val Gln Lys Ala Pro Gly Leu Val Val Ala Val Val Leu Gly 395

4

Leu Gly Ala Leu Thr Ile Pro Ala Met Asn Leu Gln Leu Ser Leu Pro Ser Asp Ser Thr Ser Asn Ile Asp Thr Thr Gln Arg Gln Ser Ala Asp Leu Met Ala Glu Gly Phe Gly Ala Gly Val Asn Ala Pro Phe Leu Val Ile Val Asp Thr His Glu Val Asn Ala Asp Ser Thr Ala Leu Gln Pro Leu Ile Glu Ala Gln Glu Pro Glu Glu Gly Glu Phe Asp Arg Glu Gln Ala Ala Arg Phe Ala Thr Tyr Met Tyr Val Thr Gln Thr Tyr Asn Ser Asn Ile Asp Val Lys Asn Ala Gln Ile Ile Ser Val Asn Asp Asp Phe 505 Thr Ala Ala Gin Ile Leu Val Thr Pro Tyr Thr Gly Pro Ala Asp Lys Glu Thr Pro Glu Leu Met His Val Leu Arg Ala Gln Glu Ala Gln Ile Glu Asp Val Thr Gly Thr Glu Leu Gly Thr Thr Gly Phe Thr Ala Val Gln Leu Asp Ile Thr Glu Gln Leu Glu Asp Ala Met Pro Val Tyr Leu Ala Val Val Gly Leu Ala Ile Phe Leu Leu Ile Leu Val Phe Arg 585 Ser Leu Leu Val Pro Leu Val Ala Gly Leu Gly Phe Leu Leu Ser Val 600 Gly Ala Ala Phe Gly Ala Thr Val Leu Val Trp Gln Glu Gly Phe Gly Gly Phe Val Asn Thr Pro Gly Pro Leu Ile Ser Phe Met Pro Ile Phe Leu Ile Gly Val Thr Phe Gly Leu Ala Met Asp Tyr Gln Val Phe Leu 650 Val Thr Arg Met Arg Glu His Tyr Thr His His Asn Gly Lys Gly Gln 665 Pro Gly Ser Lys Tyr Thr Pro Val Glu Gln Ser Val Ile Glu Gly Phe Thr Gln Gly Ser Arg Val Val Thr Ala Ala Ala Leu Ile Met Ile Ala 690

705	a Phe Ile 710		Pro Leu	Pro Pl 715	he Ile	Lys I	le Phe 720							
Gly Phe Ala Le	eu Gly Ala 725	Gly Val	Phe Phe 730	Asp A	la Phe	Phe I	le Arg							
Met Gly Leu Va		Ser Met	Phe Leu 745	Met G	ly Lys	Ala T 750	hr Trp							
Trp Met Pro Ly 755	s Trp Leu	Asp Arg 760		Pro Se	er Leu 765	Asp I	le Glu							
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aataaggtga tgt ctt cac cgt tt Leu His Arg Ph	t gca gcc	ctt tta	gaa atg	Me ggt ac	et Thr 1 cc tgg	Pro G	iln Lys 5 tg ctg:	163						
ctt cac cgt tt Leu His Arg Ph atc atc ggc at Ile Ile Gly Me	t gca gcc e Ala Ala 10 g atc tta	ctt tta Leu Leu aaa tac	gaa atg Glu Met 15	ggt ac Gly Th	et Thr 1 cc tgg nr Trp ca gac	acc control of the second	iln Lys 5 tg ctg eu Leu 20	163						
ctt cac cgt tt Leu His Arg Ph atc atc ggc at Ile Ile Gly Me	t gca gcc e Ala Ala 10 g atc tta t Ile Leu 5 c ggt atc y Gly Ile	ctt tta Leu Leu aaa tac Lys Tyr cac ggc His Gly	gaa atg Glu Met 15 agt gga Ser Gly 30 ttt ggc Phe Gly	ggt ac Gly The gtg ac Val The ttc ct Phe Le	et Thr 1 cc tgg nr Trp ca gac nr Asp tc tgt eu Cys	acc common the second s	tg ctg eu Leu 20 ta acc al Thr	163 211 259						
ctt cac cgt tt Leu His Arg Ph atc atc ggc at Ile Ile Gly Me 2 cct att gcc gg Pro Ile Ala Gl	t gca gcc e Ala Ala 10 g atc tta t Ile Leu 5 c ggt atc y Gly Ile	ctt tta Leu Leu aaa tac Lys Tyr cac ggc His Gly 45	gaa atg Glu Met 15 agt gga Ser Gly 30 ttt ggc Phe Gly aat aag	ggt ac Gly The gtg ac Val The Letter Ct Phe Letter Try Try Try Try Try Try Try Try Try Tr	et Thr 1 cc tgg nr Trp ca gac nr Asp tc tgt eu Cys 50 ca ttc	acc control of the co	tg ctg eu Leu 20 ta acc al Thr ca gcc la Ala	163 211 259						
ctt cac cgt tt Leu His Arg Ph atc atc ggc at Ile Ile Gly Me cct att gcc gg Pro Ile Ala Gl 40 atc acc atc ac Ile Thr Ile Th	t gca gcc e Ala Ala 10 g atc tta t Ile Leu 5 c ggt atc y Gly Ile c gtg tgg r Val Trp	ctt tta Leu Leu aaa tac Lys Tyr cac ggc His Gly 45 atc aat Ile Asn 60 tct gtt	gaa atg Glu Met 15 agt gga Ser Gly 30 ttt ggc Phe Gly aat aag Asn Lys atc ccg	ggt ac Gly The gtg ac Val The Le ttg ac Trp The ttg gg ac Trp Trp Trp Trp Trp Trp Trp Trp Trp Trp	et Thr 1 cc tgg nr Trp ca gac nr Asp tc tgt eu Cys 50 ca ttc nr Phe 65	acc command of the co	tg ctg eu Leu 20 ta acc al Thr ca gcc la Ala ag ggt in Gly	163 211 259 307						

tca gat ccg tcc gaa aag cca cac act ttc ttt gac aag atc ttg Ser Asp Pro Ser Glu Lys Pro His Thr Phe Phe Asp Lys Ile Leu 105 110 115	gct 451 Ala												
caa ttg gtc agg cac cca atc cga tcc att tta att ctg ctg gtg Gln Leu Val Arg His Pro Ile Arg Ser Ile Leu Ile Leu Leu Val 120 125 130	att 499 Ile												
atc gcc gtc gtc ttc tct atc ttg ctg gcg atg gga cca cct tat Ile Ala Val Val Phe Ser Ile Leu Leu Ala Met Gly Pro Pro Tyr 135 140 145	gat 547 Asp												
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Thr Asp Ala Val Thr Pro Ile Ala Gly Gly Ile His Gly Phe Gly 35 40 45	Phe												
Leu Cys Phe Ala Ala Ile Thr Ile Thr Val Trp Ile Asn Asn Lys 50 55 60	Trp												
Thr Phe Pro Gln Gly Ile Ala Gly Leu Ile Val Ser Val Ile Pro 65 70 75	Trp 80												
Ala Ala Leu Pro Phe Ala Leu Trp Ala Asp Lys Lys Gly Leu Val 85 90 95	Ala												
Gly Gly Trp Arg Phe Ser Asp Pro Ser Glu Lys Pro His Thr Phe 100 105 110	Phe												
Asp Lys Ile Leu Ala Gln Leu Val Arg His Pro Ile Arg Ser Ile 115 120 125	Leu												
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cta atg atc acc gcg gtc agc gag tca acg tac atc gtc atc tcc ctc Leu Met Ile Thr Ala Val Ser Glu Ser Thr Tyr Ile Val Ile Ser Leu 20 25 30	157													
gcc ggc ttc tcc ctt tat ggc ctt ggc ctc gga ctc ttc gcc acc cca Ala Gly Phe Ser Leu Tyr Gly Leu Gly Leu Gly Leu Phe Ala Thr Pro 35 40 45	205													
gtc acc gat act gcg ctt gga aca ctt ccc aaa gac cgt acc ggc gct Val Thr Asp Thr Ala Leu Gly Thr Leu Pro Lys Asp Arg Thr Gly Ala 50 55 60	253													
ggt gca ggt gta ttc aag atg tcc tct tcc ctc ggc gca gca ctc ggc Gly Ala Gly Val Phe Lys Met Ser Ser Leu Gly Ala Ala Leu Gly 65 70 75	301													
atc gca atc tcc act tca gtg ttc ctc gca ctt cgc gac ggc acc tcc Ile Ala Ile Ser Thr Ser Val Phe Leu Ala Leu Arg Asp Gly Thr Ser 80 85 90 95	349													
atc aac tcc gac gtc gca ctc gcc gga aca gtt tca ctt ggc atc aac Ile Asn Ser Asp Val Ala Leu Ala Gly Thr Val Ser Leu Gly Ile Asn 100 105 110	397													
gtt gta ttc gca gca aca gcc acc atc acc gca gca gtc ctt att cca Val Val Phe Ala Ala Thr Ala Thr Ile Thr Ala Ala Val Leu Ile Pro 115 120 125	445													
aaa gcc gct ggc aaa gtc tca caa acc agc atc acc ctt cct gag cca Lys Ala Ala Gly Lys Val Ser Gln Thr Ser Ile Thr Leu Pro Glu Pro 130 135 140	493													
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Thr Asp Thr Ala Leu Gly Thr Leu Pro Lys Asp Arg Thr Gly Ala Gly 50 55 60

Ala Gly Val Phe Lys Met Ser Ser Leu Gly Ala Ala Leu Gly Ile 65 70 75 80

Ala Ile Ser Thr Ser Val Phe Leu Ala Leu Arg Asp Gly Thr Ser Ile 85 90 95

Asn Ser Asp Val Ala Leu Ala Gly Thr Val Ser Leu Gly Ile Asn Val 100 105 110

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att gat gtc ctc gcc gac ccg atc gat ggc acc cca ctt gta ggc gcc 163

Ile Asp Val Leu Ala Asp Pro Ile Asp Gly Thr Pro Leu Val Gly Ala

10 15 20

gaa gat ttc tca cgg ttg gtg tct gaa tct ggg cat tcc tac gat gtt 211 Glu Asp Phe Ser Arg Leu Val Ser Glu Ser Gly His Ser Tyr Asp Val

gct cgt caa ggg tat gtc acc ctg gct ggt ggc gca ggt ctg cgc tat 259
Ala Arg Gln Gly Tyr Val Thr Leu Ala Gly Gly Ala Gly Leu Arg Tyr
40
45

tca ggc gat gat gca cag atg atc gcg gat cgg gaa acc ttc ctt tct 307 Ser Gly Asp Asp Ala Gln Met Ile Ala Asp Arg Glu Thr Phe Leu Ser 55 60 65

ggc ggt cac ttc gcg ccc ttc gtg gaa gct gtc acc gag cat gtt caa 355 Gly Gly His Phe Ala Pro Phe Val Glu Ala Val Thr Glu His Val Gln 70 75 80 85

gat gtc gtt gac cag gca ggc ctt agc gat gac gca cag cca gtg gtc 403 Asp Val Val Asp Gln Ala Gly Leu Ser Asp Asp Ala Gln Pro Val Val 90 95 100

tgc gaa atc ggc gcg gga acc ggc tac tac ttg tcc cat acc ctt gat

Cys Glu Ile Gly Ala Gly Thr Gly Tyr Tyr Leu Ser His Thr Leu Asp

105

110

115

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gca aag cgt ttg gca aag tgt cac cct cgc gtc ggc gca gtc atc gcg 547 Ala Lys Arg Leu Ala Lys Cys His Pro Arg Val Gly Ala Val Ile Ala 135 140 145

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20 25 30

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Ala Gly Leu Arg Tyr Ser Gly Asp Asp Ala Gln Met Ile Ala Asp Arg

Glu Thr Phe Leu Ser Gly Gly His Phe Ala Pro Phe Val Glu Ala Val

Thr Glu His Val Gln Asp Val Val Asp Gln Ala Gly Leu Ser Asp Asp

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95

90

Ala Gln Pro Val Val Cys Glu Ile Gly Ala Gly Thr Gly Tyr Tyr Leu

Ser His Thr Leu Asp Ser Val Ala Gly Ser Arg Gly Ile Gly Ile Asp

Val Ser Val His Ala Ala Lys Arg Leu Ala Lys Cys His Pro Arg Val

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ctt gta gat cca tat tta att gaa aat tta cgc aat gca gac ggt gaa Leu Val Asp Pro Tyr Leu Ile Glu Asn Leu Arg Asn Ala Asp Gly Glu

att gtt aaa tot tat gat aac oga goa ttt gtt aga aca atg gat aaa 192 Ile Val Lys Ser Tyr Asp Asn Arg Ala Phe Val Arg Thr Met Asp Lys

tta ggt tat aaa cac caa ggt ttc cct gta ggt tat gat tca atg agc Leu Gly Tyr Lys His Gln Gly Phe Pro Val Gly Tyr Asp Ser Met Ser 65

288 caa atc cgt tgg ctg tca gtg tta gat tta aaa gat aag act gaa gac Gln Ile Arg Trp Leu Ser Val Leu Asp Leu Lys Asp Lys Thr Glu Asp

336 caa ctt tta aaa gaa atg gat tat caa acg aga cgt aat att aaa aaa Gln Leu Leu Lys Glu Met Asp Tyr Gln Thr Arg Arg Asn Ile Lys Lys 105 100

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caa Gln	act Thr 130	Phe	tto Pho	e As _l	c tta p Le u	tto Phe 135	His	ato Met	g gct : Alá	gaç a Glu	g gaa Glu 140	Lys	g cac His	ggt Gly	ttc Phe	432
aaa Lys 145	Phe	cgt Arg	gaq Glu	y tta 1 Lei	a cca ı Pro 150	Tyr	ttt Phe	gaa Glu	a gaa 1 Glu	a ato 1 Met 155	Gln	aag Lys	tta Leu	tac Tyr	gat Asp 160	480
gac Asp	cac His	gcc Ala	atç Met	tta Lev 165	Lys	ttg Leu	gcg Ala	tat Tyr	att Ile	Asp	tta Leu	aac Asn	gag Glu	tat Tyr 175	tta Leu	528
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Leu	Val	Asp 35	Pro	Tyr	Leu	Ile	Glu 40	Asn	Leu	Arg	Asn	Ala 45	Asp	Gly	Glu	
Ile	Val 50	Lys	Ser	Tyr	Asp	Asn 55	Arg	Ala	Phe	Val	Arg 60	Thr	Met	Asp	Lys	
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Gln	Ile	Arg	Trp	Leu 85	Ser	Val	Leu	Asp	Leu 90	Lys	Asp	Lys	Thr	Glu 95	Asp	
Gln	Leu	Leu	Lys 100	Glu	Met	Ąsp	Tyr	Gln 105	Thr	Arg	Arg	Asn	Ile 110	Lys	Lys	
Thr	Tyr	Asp 115	Ile	Gly	Val		Thr 120	Lys	Thr	Leu	Thr	Ile 125	Asp	Glu	Thr	
Gln	Thr 130	Phe	Phe	Asp	Leu	Phe 135	His	Met	Ala	Glu	Glu 140	Lys	His	Gly	Phe	
Lys 145	Phe	Arg	Glu	Leu	Pro 150	Tyr	Phe	Glu	Glu	Met 155	Gln	Lys	Leu	Tyr	Asp 160	

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Lys Thr Leu Gln Leu 180

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att aat ccg tgg ttg agt gtg gct gtg ctg att ggt gga ccg ctg ctg

547

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Gln Asp Pro Arg Gly Phe Ala Gly Lys Glu Arg Thr Ala Gly Gly Leu

Leu Ser Ile Ala Ser Ser Asp Thr Gln Arg Val Gly Asp Ile Val Met

Met Thr Val Phe Pro Val Ala Glu Leu Ala Ser Ile Ile Tyr Gly Ala Val Val Met Tyr Ser Ile Asn Pro Trp Leu Ser Val Ala Val Leu Ile 135 Gly Gly Pro Leu Leu Val Val Val Ala Ile Gln Val Ser Lys Pro Leu Gln Lys Arg Ser Gly Ala Arg Gln Gln Ala Val Ala Gln Ala Ala Ala Thr Ala Thr Asp Val Val Gln Gly Leu Arg Ile Leu Lys Gly Leu Gly Ala Ile Val Thr Val Arg Arg Arg Tyr Glu Ala Ile Ser Gly Glu Ala Tyr Arg Lys Thr Val His Ala Asp Ala Ala Glu Ala Arg Leu Asn Gly Val Thr Asp Ala Ala Gly Ala Ile Phe Val Ser Ala Leu Gly Ile Gly Ala Gly Phe Leu Ala Leu Gln Gly Gln Met Ser Ile Gly Asp Leu Ile 250 Thr Val Val Gly Leu Thr Gln Phe Leu Ile Met Pro Met Thr Met Leu Gly Arg Asn Val Ala Ser Arg Trp Ala Ser Ala Glu Ala Ser Ala Lys Arg Ile Arg Gly Val Leu Gly Ala Asp Phe Glu Arg Val Ser Ala His Asp Ala Asp Lys Ala Glu Glu Ile Ile Gln Gln Leu Ala Lys Gly Leu Thr Val Ile Arg Gly Thr Asp Glu Gln Leu Val Glu Val Leu Glu Gln Leu Pro Arg Thr Arg Val Ile Val Ala Pro His Ala Ala Asp Leu Phe 345 Asp Gln Ser Val Arg Asp Asn Val His Pro Val Ala Glu Val Ala Glu Lys Ala Ile Glu Val Ala Ser Cys Asp Asp Ile Pro Gly Gly Ser Ser 375 Lys Ile Val Gly Glu Gly Gly Arg Leu Leu Ser Gly Gly Gln Arg Gln Arg Val Ala Leu Ala Arg Ala Ile Ala Phe Asp Pro Glu Val Leu Val

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105 110 115

gc Al	a gc a Al	g ac a Th	ır Ty	ec ct /r Le	g tt u Le	g at u Il	c agi e Sei 125	c As	c tg p Tr	g ct p Le	g gt u Va	c gg 1 G1; 13	y Le	g tte u Le	g gtg u Val	499
ct [.]	t gt u Va 13	l Le	g gt u Va	a co l Pr	g at o Il	c at e Il 14	e Sei	g gga r Gly	a gte y Va	g gt l Va	t gc 1 Al 14	a Le	g gc u Al	t age a Sei	c aag r Lys	547
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Gl	y Ala	a Gl	n Al	a Se 17	r As _i 0	p Ile	e Met	Met	: Gly 175	, Lei	ı Arç	y Val	l Ile	180		643
Ile	e Gly	/ G1	y Gl: 18	u Arq	g Tr) Ala	Val	Lys 190	Thr	Phe	e Glu	l Lys	195	s Ser	cag Gln	691
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100 105 110

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Val Gly Leu Val Leu Val Leu Val Pro Ile Ile Ser Gly Val Val 130 135 140

Ala Leu Ala Ser Lys Gly Ile Ser Lys Arg Ser Val Thr Gln Glu 145 150 155 160

Lys Leu Ala Glu Ser Gly Ala Gln Ala Ser Asp Ile Met Met Gly Leu 165 170 175

Arg Val Ile Lys Ala Ile Gly Gly Glu Arg Trp Ala Val Lys Thr Phe 180 185 190

Glu Lys Ala Ser Gln Ala Ser Ala Arg Ala Ala Val Asp Thr Ala Val 195 200 205

Ala Ser Gly Lys Val Ala Gly Ile Gly Glu Leu Ser Ile Ala Val Asn 210 215 220

Leu Ala Ala Val Leu Leu Leu Ala Gly Trp Arg Val Thr Thr Gly Glu 225 235 240

Leu Gly Pro Gly Gln Leu Ile Ala Ile Val Gly Val Ala Val Tyr Leu 245 250 255

Ser Glu Pro Ile Arg Leu Leu Ser Asn Ser Ile Asn Ala Ser Ala Ile 260 265 270

Ala His Gly Ala Ala Glu Arg Val Ala Asn Phe Leu Asn Leu Asp Glu 275 280 285

Ser Gln Ala Gln Tyr Glu Ser Ser Glu Thr Ile Asn Asp Gly Glu Phe 290 295 300

Leu Val Ile Val Pro Pro Ala Ser Thr Leu Pro His Gly Asp Asn Ile 305 310 315 320

Leu Ala Thr Pro His Ala Ala Asp Ile Phe Glu Gly Thr Leu Arg Ser 325 330 335

Asn Ile Ser Met Asn His Glu Asp Asn Val Pro Ile Asp Pro Gln Val 340 345 350

Ile Arg Ala Ser Gly Leu Thr Asp Ile Ile Glu Val Asp Gly Leu Asp 355 360 365

Ala Pro Val Arg Asp Thr Gly Ser Asn Leu Ser Gly Gly Gln Arg Gln 370 375 380

Arg Val Ala Leu Ala Arg Ala Leu His Ala Asp Ala Glu Val Leu Val 385 390 395 400

Leu Met Asp Pro Thr Ser Ala Val Asp Ser Val Thr Glu Val Ser Ile

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105

110

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tcc caa atg ctt ttc ctg cct gcc ggg ttg gcg tta ggt gac caa Ser Gln Met Leu Phe Leu Pro Ala Gly Leu Ala Leu Gly Asp Gln 135 . 140 . 145	Phe	547
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caa cca cag gtg agc gaa cag gag cgt tct gtt tcc acc tgg aag Gln Pro Gln Val Ser Glu Gln Glu Arg Ser Val Ser Thr Trp Lys 185 190 195	Leu	691
gtg ctg gtt ccc tcc ttg gct gtt acc agt ttg tca atg act ttt Val Leu Val Pro Ser Leu Ala Val Thr Ser Leu Ser Met Thr Phe 200 205 210	Gly	739
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	Ser 245	835
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	al 25	1075
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Thr Gln Ile Phe Thr Pro Ala Ala Leu Arg Lys Ile Gly Tyr Thr Pro 50 55 60

Val Met Ala Phe Ala Ala Phe Met Leu Gly Val Pro Ala Ile Gly Tyr 65 70 75 80

Ile Phe Ser Val Glu Pro Ile Pro Val Leu Val Val Ser Ala Leu Arg 85 90 95

Gly Ile Gly Phe Gly Ala Leu Thr Val Ala Glu Ser Ala Leu Val Ala 100 105 110

Glu Leu Val Pro Val Arg Phe Leu Gly Lys Ala Ser Gly Met Leu Gly 115 120 125

Val Phe Ile Gly Leu Ser Gln Met Leu Phe Leu Pro Ala Gly Leu Ala 130 135 140

Leu Gly Asp Gln Phe Gly Tyr Asn Val Val Tyr Val Leu Gly Ala Val 145 150 155 160

Ile Ala Leu Val Ala Ala Val Met Cys Leu Arg Ile Pro Gln Val Lys 165 170 175

Ala Ala Ala Lys Gln Gln Pro Gln Val Ser Glu Gln Glu Arg Ser Val 180 185 190

Ser Thr Trp Lys Leu Val Leu Val Pro Ser Leu Ala Val Thr Ser Leu 195 200 205

Ser Met Thr Phe Gly Ala Val Ser Ser Phe Leu Pro Ala Ala Val Ile 210 215 220

Glu Leu Asp Pro Gly Leu Gly Ala Ala Leu Ala Gly Ile Ile Leu Ser 225 235 240

Ile Thr Gly Gly Ser Ser Met Val Phe Arg Tyr Leu Ser Gly Val Ile 245 250 255

Ala Asp Arg Gly Val Pro Gly Thr Thr Met Ile Pro Ala Gln Ile 260 265 270

Ile Gly Phe Leu Gly Val Val Leu Ile Thr Val Thr Ile Phe Gln Gly 275 280 285

Trp Ser Val Trp Leu Leu Ile Ile Gly Ala Val Met Phe Gly Gly Ala 290 295 300

Phe Gly Met Val Gln Asn Glu Ala Leu Leu Ser Met Phe Phe Arg Leu 305 310 315 320

Pro Arg Thr Arg Val Ser Glu Ala Ser Ala Ile Trp Asn Ile Ala Phe 325 330 335

Asp Ser Gly Thr Gly Ile Gly Ser Phe Leu Leu Gly Ile Val Ala Ala 340 345 350

Ser Leu Ala Tyr Ser Gly Ala Phe Gly Ser Gly Ala Val Val Ile Leu 355 360 365

Phe Gly Ile Val Leu Thr Thr Ala Asp Arg Ile Ile Gly Arg His Arg 370 375 380

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ggc ggt ttg atg acg tcc ctc gga cta gtg ttg gcc atc gtg gct gtg 259 Gly Leu Met Thr Ser Leu Gly Leu Val Leu Ala Ile Val Ala Val 40 45 50

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				gag Glu												787
ctc Leu 230	gat Asp	ctg Leu	cac His	caa Gln	aat Asn 235	tcc Ser	cac His	cat His	gtt Val	tat Tyr 240	ggc Gly	ggt Gly	gga Gly	tat Tyr	gat Asp 245	835
tcc Ser	tac Tyr	ctt Leu	gag Glu	gaa Glu 250	cgc Arg	gca Ala	gtg Val	cta Leu	cgc Arg 255	cag Gln	cac His	gcc Ala	cgt Arg	gac Asp 260	caa Gln	883
				gcg Ala												931
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280 285 290 gca cct gac aac gac aaa ctt cgg aag aaa gcc gct gcg gaa tcc agt 1027 Ala Pro Asp Asn Asp Lys Leu Arg Lys Lys Ala Ala Ala Glu Ser Ser gaa aag cag get caa aaa gte ege cag atg gaa age ege ate get egg 1075 Glu Lys Gln Ala Gln Lys Val Arg Gln Met Glu Ser Arg Ile Ala Arg tta gaa gaa gtt gaa gag cca cgt aaa gaa tgg aaa ctg cag ttc agc 1123 Leu Glu Glu Val Glu Glu Pro Arg Lys Glu Trp Lys Leu Gln Phe Ser 330 335 340 gtc ggt aag gcg tcg cgg tca agt tct gtt gtt tcc acg ttg aat gat 1171 Val Gly Lys Ala Ser Arg Ser Ser Ser Val Val Ser Thr Leu Asn Asp 345 350 gca agc ttc acc caa ggc gat ttc acc ttg gga cca gta tcc atc caa 1219 Ala Ser Phe Thr Gln Gly Asp Phe Thr Leu Gly Pro Val Ser Ile Gln 365 gta aat gct ggc gat cgc att ggc atc aca gga ccc aac ggt gct ggt 1267 Val Asn Ala Gly Asp Arg Ile Gly Ile Thr Gly Pro Asn Gly Ala Gly 375 380 aaa too aca ttg ctg cgc gga cta ttg gga aac caa gaa ccc acc agc 1315 Lys Ser Thr Leu Leu Arg Gly Leu Leu Gly Asn Gln Glu Pro Thr Ser 395 400 ggt act gcc acg atg ggc acg agc gtg gcg atc gga gaa atc gat cag

1363

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aag Lys	cat His	gtt Val 440	Pro	gac Asp	tta Leu	ccg Pro	ato Ile 445	Ser	gag Glu	gtg Val	cgc Arg	aca Thr 450	Leu	ctc Leu	gcg Ala	1459
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Val	Gly	Val 35	Val	Gly	Val	Asn	Gly 40	Ala	Gly	Lys	Ser	Thr 45	Phe	Leu	Lys	
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Trp	Met 130		Ser	Gly	Ala	Ala 135		Leu	Asp	Glu	Arg 140		Pro	Ile	Val
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His	Ala	Arg	Asp 260	Gln	Tyr	Glu	Glu	Phe 265	Ala	Glu	Lys	Lys	Lys 270	Asp	Leu
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Ser	Arg	Ile	Ala	Arg 325	Leu	Glu	Glu	Val	Glu 330	Glu	Pro	Arg	Lys	Glu 335	Trp
Lys	Leu	Gln	Phe 340	Ser	Val	Gly	-	Ala 345	Ser	Arg	Ser	Ser	Ser 350	Val	Val
Ser	Thr	Leu 355	Asn	Asp	Ala	Ser	Phe 360	Thr	Gln	Gly		Phe 365	Thr	Leu	Gly

Pro Val Ser Ile Gln Val Asn Ala Gly Asp Arg Ile Gly Ile Thr Gly

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caa Gln	gca Ala 295	Gly	gac Asp	acc Thr	aca Thr	ccg Pro 300	Leu	ttc Phe	ggt Gly	att Ile	ggt Gly 305	Leu	gca Ala	cca Pro	ttc Phe	1027
	Met										gtt Val					1075
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WO 01/00804 PCT/IB00/00922

470 475 480 485

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Asn Met Leu Val Gly Phe Ser Thr Leu Gly Asp Gly Met Asn Gln Ala 50 55 60

Ala Glu Gly Ala Thr Thr Leu Ser Asp Gly Val Gly Ser Ala Asn Asp
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Gly Ala Val Gln Leu Ala Asp Gly Ala Val Thr Leu Arg Asp Gly Ile 85 90 95

Ala Ser Ala Asn Glu Gly Ala Gln Ser Leu Ala Asp Gly Ala Ser Gln 100 105 110

Leu Asp Thr Gly Leu Gly Ser Ala Ala Thr Gly Ser Gln Thr Leu Ala 115 120 125

Asp Gly Leu Ser Ser Leu Ser Ala Gly Thr Ala Gln Leu Gly Gln Gly
130 135 140

Ala Thr Gln Val Ser Asp Gly Val Gly Gln Leu Val Asp Gln Val Ala 145 150 155 160

Pro Leu Thr Ala Tyr Val Pro Asp Ile Asn Ser Gln Leu Ile Thr Leu 165 170 175

Arg Asp Gly Ala Ala Thr Ile Ala Ser Glu Leu Ser Asp Pro Ser Ser 180 185 190

Thr Tyr Arg Ser Gly Val Asp Ser Ala Val Ser Ala Ser Gln Gln Leu 195 200 205

Ala Ala Gly Leu Gln Thr Leu Lys Asp Gly Ser Ser Gln Leu Ser Ile

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gt. Va	c ct	t at u Il	c ca e Hi	s As	c ga p Gl	a ac u Th	c gc r Al	c ga a As	t ct p Le 1	u Al	g ac a Th	g ca r Gl	g ato	c cade Glu	g cgg n Arg)	163
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664

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Pro His Thr Ile Glu Glu Gly Tyr Glu Val Ala Asp Ala Ile Ala Gln 50 55 60

Glu Asp Trp Pro Glu Leu Arg Gly Glu Leu Gly Asp Leu Leu Phe Gln 65 70 75 80

Thr Val Phe His Ala Gln Met Ala Arg Glu Ala Gly His Phe Ala Leu 85 90 95

Val Asp Val Lys Ala Ile Ser Asp Lys Met Val Leu Arg His Pro 100 105 110

His Val Phe Gly Ala Gln Ser Asn Ala Lys Ser Ala Asp Gln Gln Val 115 120 125

Glu Asp Trp Glu Val Ile Lys Ala Pro Glu Arg Ala Gly Lys Ala Gln 130 135 140

Lys Gly Val Leu Asp Gly Val Ala Leu Gly Leu Pro Ala Leu Met Arg 145 150 155 160

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tg:	t gt s Va	c tc l Se	c aa r Ly 2	s Il	t gaa e Gli	a aa ı Ası	c aa n Ly	a tt s Le 3	u Ası	t gga	a tto y Leo	g gat u Asp	ggc Gl ₃ 35	/ Val	gac A sp •	211
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Pro	ago Sei 55	Ly	g gto s Val	c tci L Sei	t ato	aaq Lys	As _E	cta Leu	a gto u Val	gct LAla	gca Ala 65	Val	gca Ala	gag Glu	gtt Val	307
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Val Arg Ile Ile Leu Ala Leu Arg Asn Ser Gly Glu Leu Ser Val Asn
35 40 45

His Leu Ala Asp Ile Val Asp Lys Ser Pro Ala Ala Val Ser Gln His 50 55 60

Leu Ala Arg Leu Arg Met Ala Arg Ile Val Ser Thr Arg Gln Glu Gly
65 70 75 80

Gln Arg Val Phe Tyr Lys Leu Thr Asn Glu His Ala Ser Gln Leu Val

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